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THE THYROID  
AND  
PARATHYROID GLANDS

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RICHARDSON



# THE THYROID

AND

# PARATHYROID GLANDS

BY

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*WITH SEVENTY-SEVEN HALF-TONE ILLUSTRATIONS MADE  
FROM SPECIAL DRAWINGS BY F. P. WIGHTMAN*

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## PREFACE.

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The work that has been done on the thyroid and parathyroid glands within the past ten or fifteen years has contributed to medical literature one of its most brilliant chapters. The careful elucidation of their physiological functions, the discovery of the active principle of the thyroid and its therapeutic application, has filled us with wonder and surprise. But a few years ago the most advanced text-books gave them but a passing reference and dismissed the whole subject with the vague suggestion that the gland was constructed and placed in its position by the Divine Architect of the human body as an ornament to the neck, like a bit of molding in a house or a Doric finish to a column. Later it was supposed to have some relation to the voice, or to regulate in some compensatory manner the intracranial blood supply, but nothing was known of its true function and importance.

Since Brown-Séquard and Bernard emphasized the theory of an internal secretion, which brought upon the former an avalanche of ridicule, and Sir William Gull and Murray followed in rapid succession with their startling revelations concerning the function of this "terra incognita," it has been my great pleasure to follow, with enthusiastic interest, the contributions throwing new light on this subject, and apply to practical therapeutics the facts made clear by these investigations and observations.

Following in rapid succession after the discovery of the function of the thyroid gland came the announcement that certain conditions of a grave and persistent character were due to the congenital or acquired absence or abridg-

ment of the gland, and that these were relieved by engrafting a gland from a healthy animal into the peritoneum or other parts of the body, or by injecting hypodermically a glycerin solution of the gland of the sheep, and finally that the same purpose could be accomplished by the use of the fresh gland *per orem*. Then came the discovery that the gland could be desiccated and used as any other drug with equal efficacy and with greater accuracy.

Further research soon developed the fact that still other conditions, chiefly associated with arrested, retarded or perverted development, either of a physical or psychical character, but generally both constituting what the French have called "type Lorraine" have been found to be associated with an arrested development of the organ and could be relieved by the administration of the dried gland.

It has been also demonstrated that certain functions, chiefly menstruation and gestation, demand an extra expenditure of thyroid secretion, which, if not supplied, leads to distinct symptoms, which are also relieved by the administration of the dried gland.

Not resting here, earnest investigations have shown that it is a most potent oxidizer, with all the far-reaching effects of such an agent on the animal economy, and that it is a blood pressure reducer of seemingly a more exact and reliable character than any remedy heretofore found in our *materia medica*.

Developments are also being rapidly made concerning other ductless glands and those having an internal secretion that affect the normal relation and balance of the human economy. The suprarenal gland has become a standard therapeutic agent to a less degree, but sufficient to give promise of further development in the future.

That the therapeutic applications of the pharmaceutical preparations of these glands are not more extensively

availed of in medical practice is due, no doubt, to the fact that these useful developments have not yet been crystallized into the text-books, and, being scattered through the medical literature of many languages, have not been made available to the rank and file of the profession. Appreciating the therapeutic possibilities of the animal glands, I often have occasion to regret that the brilliant results of the work that is being done along these lines has never, as far as I know, been collected into one comprehensive volume, so that it can be availed of without an amount of research with the necessary access to libraries that are not within reach of the average physician. It was on this account that I urged Dr. Richardson to give to the profession a compilation of the whole subject, adding his personal observations and the scientific researches he has made in following up the practical application, with analyses of the human gland under various conditions of mental and physical impairment, and also by his urinalyses and blood examinations, as well as the blood-pressure tests of those to whom it was being administered, especially among the insane and degenerates, while pathologist at Mount Hope Retreat.

His capacity for research, his familiarity with the several languages in which the best literature on the subject has been written, and his general versatility render him, in my opinion, most capable of doing this work, and I feel assured that his book will supply a need as much felt by the other members of the profession as by myself. I am convinced that it will be well and thoroughly done, and I am sure I can vouchsafe it a kind and generous reception.

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# THE THYROID AND PARATHYROID GLANDS.

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## CHAPTER I.

### HISTORICAL.

The use of animal organs in medicine dates from very early times. Plinius states that the Greeks and Romans used the testicles of asses and even the semen for impotence; in Albania these organs are used for the same purpose today, and also for amenorrhea. Paracelsus, in the sixteenth century, recommended the spleen for the latter condition. Among barbarous and semi-civilized peoples, as well as among the peasantry in all countries, these customs exist. The Chinese physician prescribes dried mouse and lizard; the native African uses the liver of snakes both internally and externally as an antidote for snake bite; the warrior eats the heart of the lion to give him courage. In Southern France snails are used for indigestion as well as a luxury; in Cornwall and Devonshire earthworms are given for the same purpose. In the *materia medica*, pepsin, pancreatin, ingluvin, codliver oil and ox gall are official, all of which are animal extracts connected with the digestive functions, so that the use of other organs or their extracts is but a short step in organotherapy.

In recent times Brown-Séquard reawakened interest in the subject by his scientific experiments of removing the glands from animals and observing the result.

He argued that every gland of the body, whether it

possessed an excretory duct or not, produced a secretion which was necessary for the well being of the organism, and that it should be possible when an organ ceased to functionate to substitute the secretion of healthy glands either by transplantation, hypodermic injection of the extract or feeding by the mouth. His first attempt was the use of orchitic extract, christened "Brown-Séquard Elixir," for sterility or impaired virility. The remedy was a failure and brought much undeserved ridicule upon its advocate, but his reputation as a scientist caused others to investigate the subject, resulting in the discovery of the use of the thyroid gland in myxedema, which is one of the greatest triumphs of medicine in the nineteenth century. Brown-Séquard's statements were investigated by the Biological Society of Paris, and they reported that by the injection of semen and orchitic extract there was produced a marked increase in both mental and physical force. These experiments and the report excited the public into a belief that the elixir of life had been discovered, and that old age could be rejuvenated, with the natural consequence that pharmaceutical preparations appeared on the market with the most extraordinary advertisements. Notwithstanding all this, the foundation was laid, and many workers have been steadily perfecting organotherapy, so that two glands at least, the thyroid and the adrenals, have taken a definite place in medicine.

There can be no doubt that the testicles and ovaries have a further function than to secrete the substances necessary for procreation. The effect of castration on the mental and physical condition is well known. In those castrated before puberty, as the "castratos" of Italy, there is an arrest of development, both mental and, to a certain extent, physical; the voice remains childish, while their physical appearance and mannerisms are those of an overgrown child, with a tendency to effeminacy. Those

castrated after puberty are heavy, sullen, suspicious-looking men, without energy or ambition, while as a rule their mentality is below the average.

Whatever may be the active agent in the testicles, the absence of which produces these results, it has so far been impossible to supply its place by the use of Brown-Séquard's extract. The experiments of Fürbringer and Pulawski in Germany and Féré, Baudin, Bouffée in France gave only negative results.

The Russian chemist, Poehl, after much careful analysis, extracted spermin from the testicle. He found that the ovaries, salivary glands, thyroid, liver, spleen, and probably the brain substance, also contained spermin in small quantities, and argued that this substance circulated in the organism and was of physiological importance. A vast amount of experimental work was carried out by Tarchanow and others. They found that the resistance of the nerve centers was increased, so that the convulsions of strychnin and tetanus were controlled, and also that young dogs injected with spermin developed more quickly and better than the control animals. They summarized their results by saying that spermin was an energetic stimulant of the nervous system and probably also of other organs, and that it increased the muscle force by raising the blood pressure.

Ovarian extract has several advocates. Muret gives four reasons for its use: (1) without ovaries there is no uterine development or menstruation; (2) ablation of ovaries in young children causes them to grow up without feminine attributes; (3) after puberty loss of ovaries entails cessation of menstruation and atrophy of genital organs; (4) osteomalacia is sometimes cured by oöphorectomy. The extract has not come into general use, but there seems to be considerable evidence of its value during the menopause, in some cases of chlorosis and in

dysmenorrhea. At Mount Hope Retreat it was tried in some nervous and mental cases said to be the result of laparotomy and in a few other cases where it was thought genital trouble existed without any apparent beneficial results. In a paper read before the American Medico-Psychological Society in 1898, Dr. R. S. Dewey stated that operations on the genitourinary organs stood first on the list of surgical operations producing mental disturbance. Considering that the most important periods of life are coincident with changes in the genital organs, and that the effect of even such a small defect as laceration of the cervix will produce very considerable nervous symptoms, it does not appear unreasonable to suppose that the normal functioning of the organs of generation is necessary for the health of the organism, and that the ovaries and testicles being secretory in their nature should supply to the system something necessary for its well being.

The thymus gland has been used in many different diseases without any very definite results. It was first given to a patient suffering from Basedow's disease in mistake for thyroid by Dr. Owens. As it produced an apparent beneficial effect, it was tried in other cases with varying results. Svehla attempted to determine its physiological effect, coming to the following conclusions: Injection into the femoral vein produced a fall in blood pressure, due to weakening or paralysis of the vasoconstrictors, with increase in the pulse rate, due to direct influence on the heart; large doses produced an excitement, dyspnea and collapse, ending in death with postmortem evidence of asphyxia.

Baumann found that the thymus contained iodine in organic combination, but in much smaller quantity than the thyroid. As the thymus atrophies at puberty and its persistence after that age is pathological, being associated

with certain forms of epilepsy, and with Basedow's disease it seems improbable that its administration to the adult will produce beneficial results.

Splenic extract has not received much attention. H. C. Wood reports three cases of Basedow's disease as being benefited by it. It has also been given with benefit in cases of melancholia attonita. In leukemia it gave negative results. It is on the market as "eurythrol," but produces gastric pain and therefore does not permit of continuous use.

Bone marrow from the ribs of young animals has been extensively used in anemia without producing satisfactory results. Fraser reports its administration as having increased the hemocytes from 1,869,000 to 3,900,000 and the hemoglobin from 38 per cent to 78 per cent in 27 days.

The pituitary body is an organ which from its anatomical position would appear to belong to the central nervous system. Situated in the sella turcica, it is protected from injury, and from its glandular structure and large blood supply it should be of importance to the well being of the organism. Physiological experiments by its extirpation have so far given negative results, and, with the possible exception of akromegaly, in which it is usually found enlarged, it has not been associated with any disease. In animals after thyroidectomy it has been found enlarged by Steida, Hofmeister and Gley, but whether it is a compensatory hypertrophy has not been determined. The administration of its extract has so far produced only negative results. Anatomically, according to Andriesen, its function would appear to be to take up oxygen from the blood stream and to destroy or render innocuous the metabolic waste products of the central nervous system. Chemically it contains iodine, but in very small quantities. The last mentioned writer gives the following as the predictable results of its ablation:



Malassimilation of oxygen by the nerve tissues with accumulation of waste products, thus bringing about a nutritional failure and death of the central nervous system, when the following symptoms would be produced, depression and apathy, muscular weakness, loss of coördination and equilibration, development of twitchings and irregular contractions of the muscles, a want of sufficient heat production and consequent subnormal temperature with wasting of the body tissues.

Desiccated brain and spinal cord have been used with a few reported successes on the principle that in certain diseases the chemical processes for the formation of the specialized substances necessary for the nutrition and functioning of the nervous system may be interfered with, the administration of the brain and cord containing the specialized substances ready formed might supply the place of the lost function. Constantine Paul, Babés, Gibier, Dana and others report cases of neurasthenia, epilepsy, bulbar paralysis and chorea as benefited by its use. In Mount Hope a very obstinate case of melancholia, which had resisted the usual treatment, showed marked improvement through its use, but in several other cases no improvement was observed.

The parotid gland has been used in dysmenorrhea with reports of success, but the connection is not apparent.

Glycocholate of soda has been used with success in treating diseases of the liver, especially in hepatic colic. None of the so-called cholagogues of the Pharmacopeia increase the flow of bile, while experiment has shown conclusively that the bile salts are the only cholagogue at our command. As the bile is an excretion of the liver as well as being a necessity for the proper absorption of fats, it is of the utmost importance that the quantity should be kept at normal. The solvent action of the sodium glycocholate on cholesterin and the bile pigments render it of great

service in hepatic colic, both as preventing the formation of gall stones and also as a solvent for stone already present. It seems from various reports to be of great use in torpid liver, acting as a purge for that organ; also, in some cases of chronic constipation, in malarial and post-febrile hepatic insufficiency.

The extract of the suprarenal capsule has obtained a permanent place in medicine, the active principle adrenalin is used extensively in minor surgical operations as a hemostatic; internally it raises the blood pressure and stimulates the heart.

Extracts of the prostate gland, the liver, the kidney and the lymphatic glands have all been tried with negative results.

The thyroid gland has proved to be of the greatest importance as a regulator of the general metabolism, interference with its function producing cretinism, infantilism, myxedema and Basedow's disease, while from its powerful physiological action upon the blood-vessels the extract or the dried gland is a most valuable addition to the Pharmacopeia.

## CHAPTER II.

### EMBRYOLOGY—ANATOMY—HISTOLOGY—THE PARATHYROIDS.

*Embryology.*—The thyroid gland is developed from the anlagen, one median and two lateral, which unite to form a common differentiation. The median anlage is an invagination of the floor of the pharynx between the bases of the second and first bronchial arches lying between the two parts of the tongue and consisting of a small pouch, which commences to expand laterally at a very early age to form the median duct, the opening of which upon the tongue corresponds to the foramen cecum. The duct itself is known as the ductus thyroglossus, which persists up to the eighth week, gradually elongating as the thyroid and tongue separate. The ductus thyroglossus is obliterated, but occasionally exists throughout life as the ductus lingualis. The lateral anlagen are derived from the entoderm of the fourth gill clefts; the fourth entodermal pouch develops a ventral prolongation, becoming a closed vesicle entirely separated from the pharynx; the vesicle curves forward to form round hollow buds. The union of the three anlagen takes place about the seventh week. His records that in a human embryo of the eighth week the formation of the hollow acini had begun, and that they were lined with epithelial cells, the gland consisting of two globes connected by a narrow isthmus.

*Anatomy.*—The thyroid body is a highly vascular gland, consisting of two lobes, an isthmus and pyramid, situated between the second and sixth tracheal ring, covered anteriorly by the sternohyoid, omohyoid and sternothyroid muscles, while the sternocleidomastoid also overlaps it.

The posterior surface is concave and rests on the trachea and larynx, covering the recurrent laryngeal nerves. The



FIG. 1.—The position of the thyroid after removal of the muscles.  
(v. Eiselsberg.)

lateral lobes cover the carotid arteries; are conical in shape, extending from the fifth or sixth tracheal ring to

the side of the thyroid cartilage covering the inferior corners and adjacent portions of the alæ. The isthmus usually lies across the second and third rings of the trachea, but is inconstant in shape and position, often being entirely absent. From the isthmus or from the adjacent portions of one of the lobes a slender conical

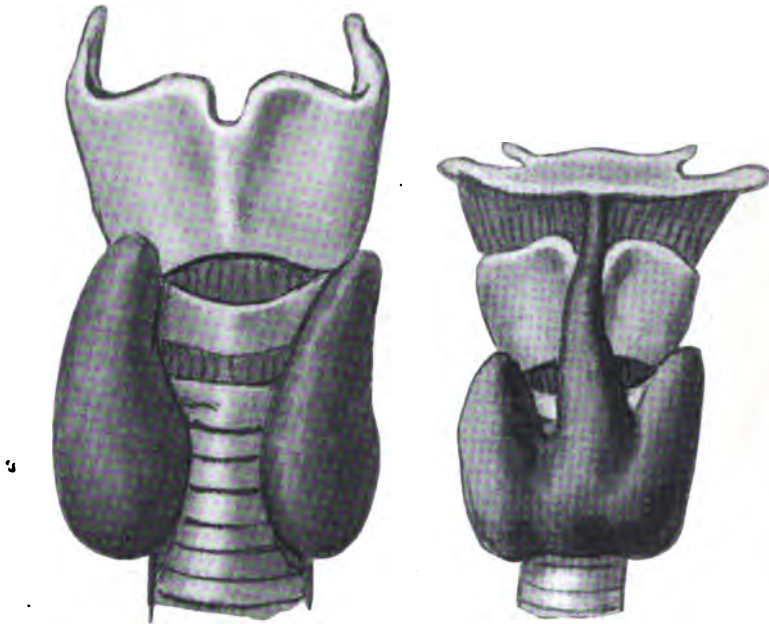


FIG. 2.—Absence of the isthmus. FIG. 3.—Isthmus with large pyramid.  
(Marshall.) (Marshall.)

process ascends upward to the hyoid bone called the pyramid or middle lobe. Occasionally it is attached to the hyoid bone by fibrous or muscular tissue, so that it follows the movements of the vocal organs. In front the pretracheal fascia extends from the isthmus and adjacent portions of the lateral lobes to the front of the cricoid cartilage, the lower border of the thyroid cartilage forming a distinct anterior ligament. Each lobe is further

attached by a firm band of fibrous tissue, the lateral ligament, to the side of the cricoid cartilage and to the first two or three rings of the trachea. Each lateral lobe measures about 50 mm. in length by 30 mm. in width by 18 mm. in thickness at its largest part. The isthmus measures nearly 12 mm. and from 6 mm. to 18 mm. in thickness. The weight of the gland varies very much with age and



FIG. 4.—Double pyramid.  
(Marshall.)

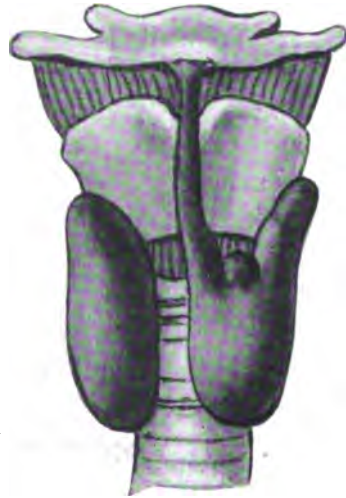


FIG. 5.—Absence of isthmus with  
pyramid on left side. (Marshall.)

in different countries. Virchow places it at from 30 to 60 grms.; Schaefer in England from 30 to 40 grms. Wells, of Chicago, gives the average weight of 60 glands removed in that city as 22 grms.; the gland decreases in weight as age advances. The average weight in persons over 45 years of age in Wells' series was only 16 grms., while in persons from 20 to 45 the average was 25 grms. The gland appears to be smaller in females than in males, increasing in size during pregnancy and menstruation.

Usually the lateral lobes are not perfectly symmetrical, the left being most often the larger of the two, while the isthmus and pyramid vary in size, may be entirely absent or fused into one or other of the lateral lobes. The pyramid occurs, according to Streckiesen, in 104 out of 153 cases or about 68 per cent. Marshall only found it in 24 out of 60 cases or 40 per cent. Out of the 104 of Streckiesen's cases it was glandular up to the hyoid bone in 55, in 12 it was connected to the bone by fibrous tissue, in 2 by muscle. These muscular fasciculi, which occasionally descend from the hyoid bone to the gland or to its pyramid, are known as the levator glandulæ thyroïdæ. The fibers are mostly derived from the hyoid muscle, but occasionally are independent.

The arteries of the gland are the superior thyroid from the external carotid, the inferior thyroid from the thyroid axis of the subclavian and sometimes the thyroidea ima from the arch of the aorta. They are remarkable for their anastomoses and large size. They terminate in a capillary network upon the outside of the acini. The veins which are also large form a plexus from which the superior middle and inferior thyroid veins are formed on each side. The superior and middle thyroid veins open into the internal jugular, the inferior veins form a plexus in front of the trachea and empty into the innominate veins.

The lymphatics of the thyroid body form numerous large anastomosing trunks, both at the surface and throughout the substances of the organ. They originate, according to Frey, in the connective tissue which unites the gland vesicles, with the cavity of which they appear not to be in communication. Hürthle has, by using intermittent pressure, caused injection fluid to pass into the vesicles by the lymphatics. Colloid substance is at times found in the lymphatics similar to that found in the ves-

icles, which appears to pass between the epithelial cells into the interstitial connective tissue and thence into the lymphatics.

The nerves are derived from the middle and inferior cervical ganglia of the sympathetic and accompany the blood vessels. According to Andriesen there are no ganglionic cells in their course, their branches extending close to the base of the epithelium cells.

Accessory thyroids are common, being formed by detachments of small portions of the gland in the embryonic stage, and by division of the pyramidal process. They may be found anywhere between the arch of the aorta and the hyoid bone, sometimes even within the bone itself.

Anomalies are common, either the pyramid or the isthmus may be absent or both, the isthmus occasionally passes behind the trachea, one lobe or both may be absent. These deviations from normal are permitted by the fact that, unlike most parenchymatous glands, the location of its secreting structure bears no relation to any fixed outlet or duct.

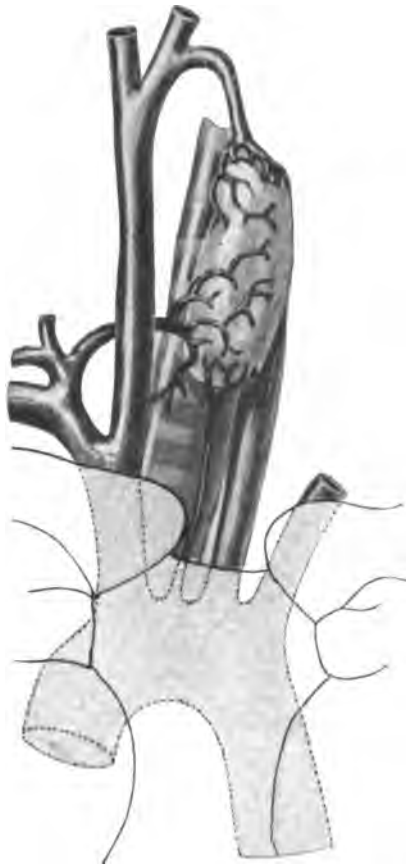


FIG. 6.—The thyroid arteries.  
(v. Eiselsberg.)



*Histology.*—The texture of the thyroid gland is firm, appearing granular to the naked eye; it is invested by a thin transparent layer of dense areolar tissue which connects it with the adjacent parts, imperfectly separating its substance into small lobules of irregular form and size. When the organ is cut into a yellow glossy fluid, colloid, escapes from the cut surface. Imbedded in its substance



FIG. 7.—Normal thyroid gland.

are multitudes of closed vesicles, which are held together in groups or imperfect lobules of areolar tissue. The wall of each vesicle consists of a simple layer of cubical or columnar epithelial cells, which, according to Langendorff, are of two kinds, viz: those which are actually secreting the material contained in the vesicles, colloid cells, and other re-

serve cells which may take the place of the colloid cells or which may become detached and mingle with the secretion. Both Langendorff and Hürthle agree in stating that the secretion is formed partly by exudation from the cells and partly by their complete transformation into colloid substance. Bozzi describes three classes of cells, chief cells, colloid cells and cells undergoing retrograde metamorphosis. The chief cells are the most numerous and contain highly refractive bodies which he considers to be colloid substance; they also contain finer bodies, which are probably incompletely formed colloid, but Babés and others state them to be the pigment from the destroyed red corpuscles; fat globules and protoplasm granules are also present. The cells appear not to have a distinct membrane, but to blend with one another, the outer ends resting on the basement membrane. The colloid cells are

smaller than the chief cells and lie in irregular groups between the chief cells from which they are probably derived; they possess a nearly homogeneous protoplasm more deeply colored, not unlike the colloid substance in appearance; they vary in shape, some appearing round or oval, with the protoplasm almost destroyed, its remains collected around a central mass which appears to be colloid containing characteristic vacuoles, the nucleus being at one side; they also group together so as to resemble follicles; sometimes free colloid is found between the cells. The cells showing retrograde metamorphosis have no colloid mass, the nucleus loses its staining properties and gradually becomes indistinct, the granules are smaller and the protoplasm contains colloid in droplets not running together to form a mass; these cells are formed when the follicles fuse together and seem to be due to nutrition degeneration.

Embryonal rests are also found mostly near the capsule, but also scattered around in the connective tissue having large nuclei with a small amount of protoplasm, they do not appear to develop when the gland is partially removed.

The method of colloid formation has not yet been settled. Virchow was of the opinion that it was first formed indirectly by the cells in so far that the secreted mucoid fluid was changed into colloid. Hürthle claimed to have seen droplets of colloid in the cells, and that the cells increased in size on the formation of the drops, concluding that the colloid arose from the protoplasm of the cells. Langhans, Langandorff, Gutknecht and others are of the opinion that the cells themselves are transformed into colloid.

#### THE PARATHYROIDS.

The parathyroids consist of two pairs of small glandular masses, first described by Sandström in 1880, constant in man and other mammals, always lying in close proximity

to the lateral lobes of the thyroid body. They vary in size from 3 mm. to 15 mm. in diameter with an average of about 6 mm.; are flattened and of a reddish color, somewhat like the thyroid itself. In structure, however, they differ from the thyroid proper, being composed of solid masses of epithelial-like cells, which often appear to be



FIG. 8.—The position of the parathyroid glands. (Zuckerkandl.)

in sections, arranged in anastomosing columns with numerous convoluted blood vessels between them. Connected with the cell masses there are frequently lymph follicles, differing completely from the thyroid and not to be confounded with the accessory thyroids. According to Gley they represent embryonic portions of the true gland, and if left after the removal of the latter they are able to develop further and take on the functions of the main organ. It is thus he accounts for the failure to obtain in some animals the usual results of thyroidectomy. This is,

however, denied by Edmunds, although they appear to increase in size after the operation and to act vicariously to some extent. Kohn states that there is one parathyroid (outer epithelial body) constantly present in mammals on the lateral surface of each lateral lobe and another on each mesial surface (the inner epithelial body). Associated with these are small bodies of adenoid tissue which have the characteristics of thymus gland including

the epithelial rests or corpuscles of Hassel and which tend to blend insensibly with the neighboring interstitial tissue of the thyroid. According to Pienant the tissue of the parathyroids is similar in appearance and structure to that of the carotid glands and is not embryonic thyroid tissue. He states that they take their origin from the fourth inner bronchial cleft of the embryo from which also part of the thymus and the lateral rudiments of the thyroid are derived, whereas the main portion of the thymus and the carotid glands are derived from the third cleft.

The theory that the parathyroids are embryonic tissue is hardly tenable, from the fact that they develop in chronological advance of the thyroid. It must also be considered that they resemble the suprarenal, the anterior pituitary and the carotid glands, which must be looked upon as adult tissue. In structure they seem to be made up of entodermal epithelial cells, separated by capillaries, suggestive of the suprarenal. This is most noticeable in compensatory hypertrophy, but, as Edmunds points out, there are no acini and no secretion of colloid substance. Gley has recently taken up the position, supporting it by physiological experiment, that the parathyroids are glands *sui generis* and have a specific function related to that of the thyroid. Welch describes the parathyroids as being completely invested by a fibrous capsule and either connected with the thyroid gland by a pedicle of fibrous tissue or situated within the body of the gland, but always completely separated from it by connective tissue. From the deep surface of its fibrous capsule irregular septa are given off, dividing the gland into irregular lobules. Clusters of fat cells are generally present along the course of the vessels and of the connective tissue septa within the gland to which the yellow tint is probably due.

The parathyroids are of epithelial structure and are composed of two distinct kinds of cells. The principal

cells have a relatively small homogeneous protoplasmic body, which takes on basic anilin dyes in varying degrees of intensity, and a relatively large pale nucleus with an open chromatin network. They constitute the greater part of the gland tissue. In their arrangement they show at least four different types: (1) a continuous uniform cell mass; (2) a continued cell mass, interrupted at frequent intervals by strands of

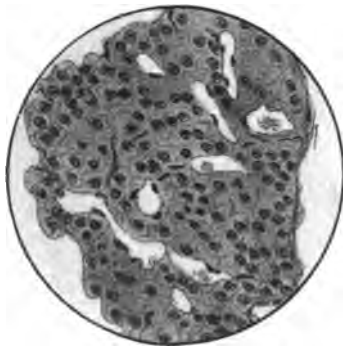


FIG. 9.—Normal Parathyroid gland.

connective tissue, so that on section the strands appear to be surmounted by epithelial cells; (3) a series of anastomosing columns of cells in a vascular fibrous reticulum, so that on section the epithelial cells appear as discrete masses completely surrounded by vascular connective tissue; (4) groups of small acini,

each containing a small mass of colloidal material in its lumen and lined by a single layer of epithelial cells. It seldom happens that a parathyroid is composed of cells exclusively arranged in one type. The second kind of cell is oxyphilic, having relatively to the principal cells a large granular protoplasmic body, the granules of which are highly oxyphilic, with a small darkly staining nucleus and densely arranged chromatin. These cells are not always present. There are three types of disposition: (1) a uniform cell mass, sharply defined from the principal cells and situated either deep in the substance of the gland or immediately beneath its capsule; (2) a few columns of cells which gradually mix with the principal cells; (3) a single acini lined with oxyphilic cells containing a colloid lobule in the lumen. Welch considers that the para-

thyroids resemble the anterior lobe of the pituitary body more than the suprarenal and that it is unlike thyroid tissue; that the colloid material does not represent a higher stage of glandular development, but is rather retrograding or degenerative in its nature.

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## CHAPTER III.

### PHYSIOLOGY.

The early physiologists looked upon the thyroid gland as having no essential function, probably from its having no duct by which its secretion could be conveyed to the general system, and from its variable size, position and shape, it was stated to be for the purpose of rounding out the neck, as having some connection with sleep, as influencing the voice, that it acted as a reservoir for the blood regulating the brain supply. The connection of the gland with the organs of generation had very early attracted the attention of the laity. In Southern Italy it has long been the custom for the parent to measure the circumference of the daughter's neck before and after marriage, an increase in size being considered as an evidence of conception.

It was not till 1859 that systematic investigations as to the function of the gland were commenced. Schiff performed thyroidectomy on dogs and found that they invariably died, and therefore the gland was necessary to life. A. and J. Riverdin described the symptoms produced by thyroidectomy, Ord followed in 1878, and then Kocher on the same lines, stimulating Schiff to further experiments. Schiff reported in 1884 that the extirpation of the gland was not only followed by death to the animal, but that it also produced spasms and convulsions, which were prevented by the implantation of the gland under the skin or in the peritoneal cavity. These experiments were the commencement of an enormous amount of work by a large number of scientists in every country,

resulting in a number of different theories as to the physiology of the organ, many of which have been proved to be erroneous and are now of little interest except to the historian.

The function of the thyroid gland is said to commence "in utero," or soon after birth (Wölfler). Horsley considers that it commences before birth, but is greatest during the period of growth, lessening as the vital processes decline. He bases his opinion on the decrease of the secretory power of the gland in phthisis, in which the colloid substance gradually disappears and the epithelial cells pass into the embryonic state, from the fact that removal of the gland is more fatal in young than in older animals, and that it decreases both in size and activity in old age. Nielsen is of opinion that the gland is concerned in the change of mucoid into connective tissue during the fetal months.

The writer has analyzed the thyroid glands of several children who died immediately after birth, and also a few prematurely born, and has never been able to find a trace of iodine or of the blood pressure reducing substance. In children of two and three weeks old who had died of cachexia, no iodine was found. The earliest age at which he found iodine was three months. There is a remarkable difference between the calf and the human fetus. In the former the thyroid gland contains iodine in utero. As it has been shown that thyroglobulin is excreted by the mammary gland, with the milk in the human, the child receiving in this manner the necessary amount for its metabolism, it seems possible that one of the reasons why the human infant is so difficult to raise on artificial food is the absence of the necessary amount of thyroid secretion in the artificial food. As the calf is born with a functioning thyroid, cow's milk probably does not contain the amount of thyroid secretion necessary for the development of the infant.



The function of the gland has been studied chiefly by the indirect method of observing the symptoms after removal of the gland from animals, and some cases in man, where the operation was performed for disease. In the early experiments the importance of the parathyroids was not recognized, and consequently the symptoms were the result of the removal of both thyroid and parathyroids, which has caused much confusion, being further complicated by the different results obtained with different animals—in some instances as in the rabbit—due to the parathyroids being some distance from the thyroid and not being removed in the operation with the thyroid. Ewald came to the conclusion that birds survived the operation; that rodents and herbivora generally survived with no marked effects, and that in aged dogs the symptoms were usually light. Reptiles, young carnivora, monkeys and man invariably die after the operation if it is completely carried out. Horsley, in 1891, divided animals into four classes: (1) birds and rodents, in whom no cachexia was produced; (2) ruminants and ungulates, in whom the symptoms developed slowly; (3) man and monkeys, in whom the cachexia was certain but the symptoms moderate; (4) carnivorous animals, in whom the cachexia was most severe and rapid. These results seemed to show that the food habits of the animals had some bearing on the importance of the gland to the system, viz: that carnivora were the most affected, graminivorous and corn eating animals the least affected, while the omnivora occupied a middle position. The later experiments of Hofmeister, de Quervain, Gley and Edmunds have shown that there is little or no difference, provided that the whole of the thyroid, accessory thyroids and parathyroids are removed.

The symptoms produced by the extirpation of the gland are of particular interest from their resemblance to vari-

ous observed pathological conditions in man, and have been the means of recognizing many obscure diseases as being the result of cessation or perversion of function of the glands.

In dogs, after the removal of the gland, the first most noticeable symptom is a derangement of the functions of the medulla oblongata, consisting in vomiting and dysphagia. The efforts of vomiting are accompanied by salivation, often preceding an attack of convulsions lasting till the animal dies. The vomited matter consists of bile and mucus; anorexia is often present, and when the refusal to take food is absolute it is a sure sign of a rapidly fatal result. Sometimes the animal preserves the appetite but finds great difficulty in taking nourishment, owing to the continuous spasmodic contractions of the masseter and the fibrillar contractions of the muscles of the tongue. Moreover, the dysphagia usually present renders it as difficult to swallow fluids as solids, and if by chance any food does enter the stomach it is immediately rejected, with an increase of convulsive movements, the animal finally ceasing to make any attempt to take food. Vomiting occurs even when the food is carefully introduced with the tube. In a few instances the animal continues to eat, but the food accumulates in the stomach, the abdomen becomes distended and the large intestine fails to discharge its contents. Trophic disturbances may appear in the form of excoriations, especially affecting the region of the articulations in the fore and hind limbs, which may suppurate, never showing any inclination to heal. Muscular paresis and partial paralysis occur usually among the earlier symptoms, the extensors in particular being affected, causing the staggering gait which is usually very marked. Spasms are of frequent occurrence, which, in the first instance, affect the masseter and temporal muscles, but soon spread to the muscles of the body, and seem

to be the result of discharges which take place at regular intervals. This condition lasts for two or three days, when a violent general convulsion may occur, with a tendency to tetanus. At this period the respiration is greatly increased, in some cases being as high as 220 per minute, death often supervening in one of these convulsions. Coincident with increase of respiration comes increase of temperature, 42.0 degrees C. and even 43.6 degrees C. having been observed. In the intervals between the attacks the temperature has been observed to fall 4 degrees below normal.

In 1887 Munk made the statement that dogs survived operations which deprived them of the functions of the thyroid gland, provided the wound healed well, but if swelling of an inflammatory or edematous nature, or a swelling dependent on hemorrhage or upon accumulations of the secretions of the wound occurred, the animals died with characteristic symptoms. Munk performed the operation of isolation of the gland by doubly ligating and dividing the veins of the gland. He then lifted the lobes out of their capsules and completely severed them from their connections with the body of the animal by ligation of the vessels and nerves of the hilus, returning the lobes to their original position. Nine dogs survived his experiments which were repeated and confirmed by Boginski. Halstead suspecting that Munk had overlooked the accessory glands and also small portions of the main gland, went over the same ground in the most complete manner, finding that his suspicions were correct. He found that when the gland was perfectly isolated death ensued with the usual symptoms, which varied somewhat in different animals, the most regular being conjunctivitis, trismus, persistent erection of the penis, fibrillary tremors of the tongue and of the muscles generally. He then experimented with partial isolation, which he brought about by

ligating all the vessels except the thyroid artery, which supplies the upper lobe and the vein from the lower lobe. The symptoms thus produced were not identical with those occurring in complete isolation. The most constant were tongue tremors, licking movements, anemia, conjunctivitis, general tonic and clonic spasms, inflammation of gums, with occasionally a falling out of the hair, accompanied with an itching of the skin, producing an edematous appearance not unlike myxedema. This latter symptom only occurred when the wound did not heal by first intention. He next experimented with piecemeal removal of the gland and observed that the same symptoms were produced, the amount of gland removed in order to produce them varying in different dogs, probably on account of the size and number of the accessory glands and to individual peculiarities, one dog doing well and remaining in good health with only one-eighteenth of the gland remaining. During the experiment a female who had had the left and the lower third of the right lobe removed was impregnated by a healthy unoperated dog. She gave birth to eight puppies, whose thyroid glands were at least twelve times larger than normal. It is remarkable that in this case and also in a similar one that a few hours before whelping the symptoms of complete thyroid deprivation manifested themselves although each animal possessed much more thyroid than was actually required for her wants. It had previously been observed that tetany had appeared previous to labor in cases with congenital thyroid insufficiency. These experiments have been repeated recently with the same result by Edmunds and are suggestive. It would be interesting to observe if an excessive secretion or administration of thyroid during pregnancy would not produce a reduced thyroid in the produce, which, if it took place, might account for some cases of sporadic cretinism.

Horsley divides the symptoms of thyroidectomy into those of over action and of want of action. The first symptom of over action is fibrillar muscular tremor, resembling tetany. The individual contractions of the muscles follow one another in monkeys at the customary rate of clonus, viz: eight to ten per second. Summation next occurs, tetanoid spasms follow and finally rigidity and contraction. Symptoms of want of action are motor paralysis and anesthesia, the toxemic condition producing functional neurosis, epilepsy, hemiplegia, etc. Tissue changes are also marked, emaciation of an acute form, with mucin in the connective tissue. If, however, the cretinoid condition supervenes there is no increase of mucin, but fibroid changes occur, coupled with emaciation. Virchow suggests that the edema characteristic of myxedema is a metaplasia of the subcutaneous fat into mucus, with an increase of volume; the skin becomes coarse and dry from the absence of secretion; the subcutaneous tissue thickened and inelastic; the hair falls out, becoming thin and gray. Disorders of temperature also occur. The intrinsic changes, viz: the modifications which are introduced into the normal heat balance of the subject after elimination of the traumatic factor, consist of a rise of from 4 degrees to 5 degrees during the acme of the muscular twitching. The coincidence of this rise in temperature with the nerve disturbances suggests that it may be dependent on a derangement of the heat controlling centers. Before death the temperature is subnormal. External heat has a great effect on the operated animal, external cold precipitating the symptoms. Animals which were apparently in good health while kept in a high temperature developed the characteristic symptoms at once on being exposed to cold.

The blood changes show a connection between the gland and the blood metabolism. Normally the leucocytes are

present in a greater proportion in the veins than in the arteries of the gland, and this proportion is greater than that found in the veins of the limbs. After thyroidectomy there is an increased venosity of the blood, with a great diminution of the amount of oxygen. This decrease of oxygen in the arterial blood may be so great as to be less than the oxygen in normal venous blood, a condition which would account for many of the symptoms.

If a portion of the thyroid gland be removed there is a compensating hypertrophy of the remaining part which undergoes histological changes, the cubical cells become columnar, the vesicles become oblong or branched and the colloid substance becomes more watery, changes which are almost identical with those found in the gland in Basedow's disease. These changes are not affected by division of the sympathetic. Schiff found, after destroying the sympathetic nerve fibres accompanying the blood vessels to one lobe, that the lobe remained identical in minute structure. Horsley tried similar experiments with respect to the recurrent laryngeal nerve with the same result. Katzenstein could find no difference in the two lobes after stimulating one and not the other. Edmunds excised the superior laryngeal nerve and a considerable length of the vasosympathetic lower down on the same side, thus any secreting fibres passing by the recurrent laryngeal nerve would be cut off. On this side the thyroid lobe was not touched or even seen. On the other side the lobe, together with the parathyroids, was excised. Of the ten dogs experimented upon three died in one, two and three days. No symptoms occurred, but death appeared to be due to the operation, as the thyroid lobe was found to be almost free from colloid and the secreting cells multiplying into the vesicles. Seven of the dogs lived longer, six showing symptoms; one, however, was operated on again after twenty-eight days without having shown any

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symptoms. One was allowed to live 242 days, dying with athyroidal symptoms. Another was killed at the end of 271 days suffering from severe symptoms. The other four were operated on a second time. The pathological findings in these cases varied somewhat. In one, in which the lobe was removed by a second operation, the gland was devoid of colloid, the cells multiplying into the cavities of the vesicles. In another, which had well marked tremors but recovered, the gland was found to be much enlarged, weighing 3.5 grms., or about three or four times larger than normal. The colloid had disappeared, the increase in size being due to growth of young tissue between the vesicles, the secreting cells were not multiplying into the vesicles. The animal which lived 242 days, dying with severe symptoms, had a normal gland and a normal parathyroid. In the animal killed after 272 days there were some normal vesicles, but there were also vesicles filled with multiplying cells from which the colloid had wholly disappeared.

Hürthle has experimented on the effect of the stimulation of various nerves by the faradic current on the secretion of the gland, and has had negative results from both the laryngeal nerves and the vasosympathetic. On the contrary, G. A. Schaefer found that the cells of the thyroid show the same changes as those of other glands after the injection of pilocarpine. As pilocarpine only produces its effects by nerve stimulation it follows that the secretion of the thyroid must be influenced by the stimulation of some nerve or nerves. Hürthle suggests that the stimulation of the gland is due to the presence of certain unknown substances in the blood, and states that tying the gall duct in dogs produced homogeneous globules in the epithelial cells and lymph spaces of the gland, which showed the same inclination to solidify and gave the same staining reactions as the follicular colloid substance, prov-

ing that the passing of certain constituents of the bile into the blood produced increased secretion of the gland, and that any nervous influence that may exist is not central, but is due to the ganglia either in or in the immediate neighborhood of the gland, and further, that the enlarged gland of Basedow's disease is not primarily of central origin.

Sandstrom discovered the parathyroids in 1880, and in 1881 Cresswell Baker independently also observed the glands but did not recognize them in animals, describing them as undeveloped portions of the thyroid gland. In 1884 Horsley identified and described the parathyroids, but they were not thoroughly studied till 1892, when Gley published a set of papers recording his experiments. Under the name of "*glandes thyroïdiennes*" he described in the rabbit two glands, one on each side of the trachea, situated at some distance below the thyroid, so that in previous operations for thyroidectomy in that animal these glands had probably not been removed. In the dog, on the contrary, the corresponding structures were so closely incorporated with the outer surface of the lateral thyroid lobes that they must have been almost invariably removed with the thyroid. On account of these different anatomical arrangements he suggested the causes for the relative insusceptibility of the rabbit to thyroidectomy; he removed both the thyroids and the parathyroids from a series of rabbits with the result that in the majority of cases acute symptoms and speedy death ensued. Further, he found that the removal of the thyroid alone, leaving the parathyroids in situ, produced in the dog and the rabbit little or no result. At the time of these experiments (1892) the existence of the internal parathyroids was not known, and Gley's work only applies to the external parathyroids. No really accurate knowledge of the position of these glands was published till



1895, when Kohn's elaborate monograph on the thyroid gland of the cat demonstrated the fallacies underlying all previous operations. He found that in the cat, dog, rabbit, and probably in other mammalia, there were four parathyroids, and he further showed conclusively that these bodies were not thyroids but were independent specific structures, naming them "the external and internal epithelial corpuscles of the thyroid."

In 1896 Vassali and Generali published the result of their experiments. They removed all the four parathyroids, leaving the thyroid in situ in ten cats and in nine dogs. Of the cats nine died by the tenth day, while one was living at the end of a month. All the dogs died within eight days, the symptoms in both cats and dogs being the same as those previously recorded as the result of thyroidectomy. As a rule, however, conclusive attacks were absent or only very slight, but on the other hand, the phenomena of diminished nervous excitability predominated in the form of paralysis, which rapidly killed the animal. Rouxau performed on the rabbit what Vassali and Generali had done on the dog and cat, viz: he removed the four parathyroids, leaving the thyroid intact. The results were not uniform, but he concludes that removal of the parathyroids is much more serious than removal of the thyroid alone in the rabbit. Moussu comes to the conclusion that the functions of the thyroid and parathyroids are different; that suppression of the thyroid produces only chronic symptoms, while the suppression of the parathyroids induces acute symptoms. He also induced experimental cretinism in the dog, cat, and birds by the removal of the thyroid, the parathyroids being left intact. Welsh, after a number of very careful experiments, comes to the following conclusions: (1) Removal of all four parathyroids in the cat leads to acute and severe symptoms, with a rapidly fatal issue, even though the thy-

roid be retained practically uninjured. (2) Removal of three parathyroids does not lead to death, but may cause transient symptoms similar to those which result from removal of all the glandules; loss of two parathyroids does not produce any appreciable result. (3) Removal of the thyroid and some of the parathyroids may lead to death with acute symptoms, if only one parathyroid is left, but may not induce any obvious derangement if two parathyroids are retained, at least not for several months. (4) Administration of fresh parathyroid by the mouth has no effect, either in mitigating the symptoms or in averting death after removal of the thyroid and parathyroids in the cat, even though relatively enormous doses are given.

In 1898 Edmunds published the results of his very elaborate experiments as to the functions of the parathyroids, of which the following are the most important. In two dogs about one quarter of one lobe and the external parathyroids were left, the rest being removed. Neither of these dogs showed any symptoms during the nine and twenty-six days they were allowed to live. In two other dogs the upper part of the thyroid was left on each side, with the addition that in each a length of the vasosympathetic was removed on one side. One of the dogs suffered from tetany, rigidity of the limbs, tremors, emaciation, and a trophic lesion of the skin, in the second dog the only symptom was emaciation; twenty-nine days later the remaining portion of the gland was removed, the dog dying with the usual symptoms. In eight dogs one external parathyroid was left and only just sufficient thyroid to avoid interference with the blood supply. The dogs had no symptoms, except that one of them became thin. Three of these dogs were subsequently killed and the parathyroids identified by microscopical examination. In the other five it was attempted to remove the parathyroids during life. In two this was successfully accomplished,

with the result that the animals had the usual symptoms. In the other three dogs the part removed proved not to be parathyroids and no symptoms resulted, the parathyroids being found on postmortem examination. In seven other dogs it was intended to leave the external parathyroids, but microscopical examination proved that the tissue left was not parathyroid, all three dogs dying with the usual symptoms. As dogs live when the parathyroids are left and die when it is subsequently removed, or when only a small piece of thyroid proper is left instead, it seems evident that the excision of the parathyroids is the cause of the acute symptoms, tremors, rigidity, convulsions, dyspnea and death, which follow the total excision of the thyroid and parathyroids, and further it suggests that the excision of the thyroid proper only causes the symptoms of myxedema. In four rabbits, from which the thyroid was removed, leaving the parathyroids, the health failed, the hair fell out, edema occurred in the lower part of the face, followed by death. Vassali and Generali have found that if all the four parathyroids in the dog are excised and the whole of the thyroid left the dog will die with the usual symptoms in a few days, while if one of the parathyroids is left and the whole of the thyroid removed the animal will live. Gley found that if the whole of the thyroid proper and one parathyroid were removed in rabbits the animal would live, but if the remaining parathyroids were excised the rabbit would die with the usual symptoms. In dogs in which a single parathyroid was left and a minute piece of the thyroid no symptoms of any kind appeared, even after five months. The animals were kept so long in order to see if the parathyroids developed into thyroid tissue. They did not, but the cells became more definitely arranged in rows, small collections of secretion were seen and the trabeculae of connective tissue were much thickened.

In order to obtain an obvious case of myxedema, the whole of the thyroid gland was removed from four monkeys. In the first there was muscular weakness, the hair fell out extensively from the front of the chest and there was some swelling about the face, but only temporarily. Four and a half months after the operation a well-marked edema occurred in the face but quickly passed away, and in six and a half months the monkey was well. The other three monkeys died with the usual symptoms. The failure to obtain true myxedema in these cases was apparently caused by the animals dying from the nerve symptoms before the myxedema had time to develop. Four other monkeys were operated upon as before and treated with thyrocolloid, prepared according to Hutchinson's method. The first monkey died in six days in spite of treatment, and the second had slight symptoms on the first day which passed off. On the twenty-seventh day the treatment was stopped, three days later symptoms appeared but passed off, when treatment was renewed, the animal, however, dying on the forty-first day. The third monkey had no symptoms from the first; the treatment was stopped on the sixteenth day; on the twenty-first day symptoms appeared, treatment was resumed, the symptoms disappeared, and five months after the operation the monkey was well. In the fourth monkey symptoms appeared on the third day and the monkey died on the seventh day in spite of treatment. Though three out of four of the monkeys died yet treatment had some effect. Edmunds summarizes the results of his experiments, coming to the following conclusions: (1) the parathyroids of dogs have as much or more to do with saving them from acute myxedema as the thyroid proper; (2) although the extract from the thyroids of sheep may keep off and relieve the symptoms in thyroidless monkeys it will not, as a rule, save their lives; (3) a parathyroid will not by

process of compensatory hypertrophy develop into thyroid tissue; (4) the mortality was 44 per cent after total excision of the parathyroids, and after excision of both thyroid and parathyroids the mortality was 80 per cent, even with thyroid feeding; (5) the symptoms produced by the excision of the parathyroids are the same as by the complete operation (thyroid and parathyroids), viz: tremors, a slow and unstable gait, passing into paralysis of the hind limbs, emaciation and muscular weakness.

The microscopic changes found in the thyroid lobes in cases of excision of the parathyroids are marked in these cases which survive the operation a few days. There is a diminution in the amount of colloid in the vesicles, the vesicles themselves becoming oblong and branched, the secreting cells columnar or multiply so as to fill the cavity of the vesicle and there is an excessive amount of young thyroid tissue between the vesicle. Edmunds considers these changes to be identical with those described as compensating hypertrophy of the thyroid and with the changes found in Basedow's disease; there is, however, an apparent decrease in the size of the gland.

In two of the dogs, after partial parathyroidectomy, there were marked eye symptoms. Auld and others have noted eye symptoms after thyroid feeding, Bécclere reporting a case where a patient, partly by mistake, took 60 grms. of sheep's thyroid in a week, which was followed by thyroidismus and a certain amount of exophthalmos. Edmunds performed a number of experiments to investigate the point, the subject being of great importance from the possibility of its offering an explanation of the pathology of Basedow's disease.

Total thyroidectomy was performed on ten monkeys, five of whom had had thyroid feeding before the operation. Of the five which had no thyroid feeding two showed narrowing of palpebral fissure, one at first widen-

ing, followed by narrowing, and in two no change. Of the five which had thyroid feeding, in two there was exophthalmos with widening of the fissures; in one narrowing, and in two no change. In another monkey no operation was performed, but it was fed with large doses of an extract equal to about half a sheep's thyroid per diem. A considerable widening of the palpebral fissures resulted, with perhaps some protrusion of the eyeballs. Edmunds, in further experiments on six monkeys fed with from a half to three whole sheep's thyroids per day, produced proptosis, dilatation of the pupils, widening of the palpebral fissure, erection of the hairs of the head, falling out of the hair in patches, paralysis of one or more limbs, emaciation and muscular weakness, followed by death from asthma. The average life of the monkeys after the commencement of the treatment was seventy-six days. Microscopic examination of the thyroids and of pituitary glands were made, but no pathological condition could be detected. Shortly before death the animal showed an objection to light and to being looked at.



FIG. 10.—Monkey in tetanic attack after extirpation of thyroid. (v. Eiselsberg.)

As the effect of thyroid feeding on the eye might be produced by action on the central nervous system, communicating with the cervical sympathetic or by local action

on the ganglia in and about the eye, the cervical sympathetic was divided on one side in two monkeys and the animals fed in doses corresponding to about three sheep's thyroids per day. In twelve days the eyes on the unoperated side were seen to be more prominent and the palpebral fissure wider than before treatment; the eyes on the operated side also became very wide and prominent. A considerable length of the nerve was removed to prevent the probability of repair. This experiment is borne out by a case reported by Boissou. The patient, a girl of twenty years old, was submitted to resection of the cervical sympathetics, first on one side and then on the other, for Basedow's disease. Notwithstanding the operation the exophthalmos continued and became so severe that the eyes could not be closed, the cornea sloughed, sight was lost, the patient dying in a short time.

This case and Edmunds' experiments show that the cervical sympathetic is not the main factor in producing the protrusion of the eyeballs, and it also seems probable that thyroid extract acts partly through the cervical sympathetic and partly locally. Experiments were also made on rabbits, with the thyroid with the two smaller parathyroids removed. In one rabbit the eyes became more prominent and remained so; in one no change was observed for nine months, when the eyes began to get narrow, becoming very narrow before death. The cervical sympathetic was excised on both sides to see if it produced further narrowing; in two the eyes became very narrow before the animals died, which occurred in two or three days; in three the eyes narrowed and the animals lived, and in one there was no change. The thyroids of the four surviving rabbits were excised, the two larger parathyroids being left intact. In one there was a marked increase in the narrowing, in the other two no immediate effect, but the animals died ten months later with very narrow eyes. In the

rabbit in which division of the sympathetic had produced no symptom, the excision of the thyroid was followed by death in three days with narrow eyes.

In further experiments to observe the effect of the excision of the parathyroid on the eye, Edmunds excised both cervical sympathetics in a rabbit, which caused narrowing of the palpebral fissures; later he excised the thyroid together with the two smaller parathyroids, leaving the two large parathyroids. This operation produced no further narrowing. In five rabbits he excised the two larger parathyroids, leaving the thyroid intact, together with the two smaller parathyroids. In four animals the eyes became somewhat wider for a time, reverting to normal; in one there was no change. In six rabbits the opposite operation was performed, namely, the two larger parathyroids were left intact and the thyroid lobes with the two smaller parathyroids were excised. The results varied, in three of the rabbits it was noticed that the eyes for a time were wider than normal, four of the rabbits died and, at the time of death, their eyes were much narrowed; two were killed at a time when the eyes were normal.

Edmunds summarizes his results as follows:

(1) That after complete excision of the thyroid and parathyroids the great majority of dogs die within a few days and cannot be saved by thyroid feeding, but a small minority survive even after the complete operation.

(2) In operations in which one or more parathyroids are left the dogs as a rule survive.

(3) That when only the thyroid is left they die as a rule.

(4) That with respect to operations that paralyze the secretory nerves of the thyroid the dogs often die, although possessed of the whole of one thyroid lobe, together with the parathyroids of the same side, or even as in Halstead's experiments when possessed of the whole thyroid.



(5) With respect to the microscopical appearances of the parts left in the experiments, the parathyroids seem merely to hypertrophy, and they do not change into thyroid tissue proper. The thyroid tissue may remain unaltered even though the dog may die of athyroidic symptoms, or it may materially alter and this in one or two days; either the colloid diminishes or entirely disappears, vesicles enlarge and the lining membrane becomes convoluted. This may occur to such a degree as to present appearances closely resembling, if not identical with, those in a papilloma, or the colloid may disappear, the vesicles may retain their shape and the round cells may multiply into and fill the cavity of the vesicles, thus producing an appearance somewhat similar to that seen in carcinoma, but though much hypertrophy sometimes occurs nothing of the nature of invasion has been seen.

(6) In the central nervous system changes have been found corresponding to paralytic symptoms, the lesions that occur are observed mainly in the large cells, varying from chromatolysis of the Nissl granules to a complete destruction of the cells.

(7) In the eyes of monkeys, dogs and rabbits he finds that when an animal is dying of athyroidic symptoms, whether after a complete or only partial extirpation, there is, as a rule, narrowing of the palpebral fissures. After the removal of the parathyroids a condition of widening of the eyes occurs, which coincides with the view that Basedow's disease is connected with the parathyroids.

Moussu has experimented with the parathyroids and comes to the conclusion that the acute convulsive attacks in thyroidectomized animals are due to the parathyroids having been removed, and that if operated dogs are given the watery extract of from twelve to twenty horses' parathyroids the convulsions are arrested. He further states that myxedema is not helped by the administration of

parathyroid (confirmed by Charrin), but that he has seen improvement in a case of Basedow's disease by the injection of the extract of eight horses' parathyroids per diem. He sums up that the removal of the thyroid, leaving the parathyroids produces myxedema in man and perhaps



FIG. 11.—A 4 months old kid whose thyroid was removed at 21 days old. (v. Eiselsberg.)

FIG. 12.—Control animal from the same birth. (v. Eiselsberg.)

also in swine and dogs; in other species progressive cachexia. In the young of man, swine, goats, dogs, cats and birds it produces cretinism, which is improved by the administration of thyroid. That the removal of the parathyroids in carnivora produces death, which was formerly attributed to the absence of the thyroid, and that the par-

tial removal of the parathyroids produces symptoms similar to Basedow's disease, it has not been shown as yet that the parathyroids are diseased in Basedow's disease, nor that feeding with parathyroids will benefit the patient. A few cases are recorded, but as yet the benefit of the treatment must be regarded as "not proven."

There seems to be no doubt that the two sets of glands are not wholly independent, for the removal of the thyroids causes changes in the parathyroids, and the excision of the parathyroids changes in the thyroid. One very attractive theory suggests itself, that the symptoms of myxedema are due to the failure or removal of the thyroid, while removal or failure of the parathyroids produces the tremors and other nervous symptoms, with the general symptoms of Basedow's disease. If the failure of the parathyroids causes hypertrophic changes in the thyroid, as shown by Edmunds, it may be supposed that the increased secretion of the altered thyroid would cause exophthalmos, and thus we should have, as in Basedow's disease, tremors, exophthalmos, etc. Edmunds states that excision of the parathyroids produces sometimes exophthalmos, sometimes enophthalmos, and exophthalmos can be converted into enophthalmos by the removal of the thyroid lobes. Total thyroidectomy in the monkey is usually followed by enophthalmos, exceptionally exophthalmos, while thyroid feeding produces exophthalmos in monkeys, as a rule.

Prof. Freiherr v. Eiselsberg experimented with the removal of the thyroid in young animals. He removed the thyroid from two lambs at ten days old, keeping another as control. In a month the control animal was much larger than the operated lambs, and at six months the control animal was as heavy as both the other operated lambs together. It weighed 35 kg., compared with 10 kg. and 14 kg. Not only was the physical growth arrested,

but the mental condition was very evidently defective, and there was also a want of coördination. At the autopsy there was calcification of the aorta, which had the appearance of being due to senile changes and not to inflammation. He operated on young goats, pigs, rabbits and asses and found the same results, namely, arrest of physical and mental development, comparable to cretinism.



FIG. 13.—Lamb, 6 months old, the thyroid being removed on the tenth day. (v. Eiselsberg.)

The influence of the thyroid secretion on the morphology of the organs of generation in both sexes has been demonstrated by many observers. It is an ancient tradition that the thyroid enlarges at the first menstruation, in certain women, each period producing an appreciable enlargement of the gland. There seems also to be a balancing as it were between the flow of blood and the gland. A suppression of menstruation often produces a swelling of the gland, which disappears on the reestablishment of the flow. There is also a very remarkable connection pointed out by Gautier that the menstrual blood contains

iodin and arsenic, both of which substances are a part of the normal secretion of the thyroid. In girls it has often been stated that the first sexual act produces an enlargement of the gland. There seems to be no connection between the thyroid and the sexual act in the male, it having never been observed to swell after the first coitus but enlarges about the time of puberty and occasionally a palpable goitre may form. The enlargement of the gland during the rut has been observed in the dog, cat, rat, sheep and deer, and was described by Wagner in 1858.

The effect of the thyroid development on puberty is of great importance. Broca ("Goitre and Cretinism," 1891) states that in the complete cretin puberty is never established. The reproductive functions are nil and sterility is absolute, while arrested development of the sexual organs is almost a constant symptom of infantilism. Occasionally there are cases of hyperthyroidea occurring at puberty, which Brissaud explains as a result of a difficult sexual metamorphosis, or, in other words, that an arrested development of the sexual organs may produce thyroid derangements. In cretinism, and especially in infantilism, the increase in the development of the sexual organs under thyroid treatment is very marked. It is of importance, from a therapeutic standpoint, to note that the increase in size of the thyroid gland is anterior to the development of the sexual organs, the secretion of the gland being increased, the surplus is utilized to stimulate growth, and, therefore, if the gland does not increase, puberty does not occur and the growth is retarded, producing infantilism.

During pregnancy there is a marked modification of the gland. Freund observed augmentation of volume in forty-five out of fifty women. Lange established that the enlargement commenced about the fourth month in primiparas and the fifth month in multiparas. The gland

commences to diminish seven or eight days after confinement and quickly recedes to normal; sometimes the hypertrophy continues through lactation. Lange found that out of 133 cases 25 did not show any hypertrophy; examination showed that 20 of these presented albuminuria, and he argued that the relative insufficiency of the thyroid has an influence on the kidney. Experimentation confirmed his theory. Lange removed four-fifths of the thyroids in a



FIG. 14.—Control animal. (v. Eiselsberg.)

number of cats, producing no symptoms except in those with young, the latter dying and the autopsy showing fatty degeneration of the kidney. Several of the operated cats were impregnated, developing albuminuria and the kidney degeneration. This experiment shows a possibility of eclampsia being connected with hypothyroidia.

The thyroid has also some effect upon the production of milk. M. Wauters experimented upon a cow who, for fifteen days, had averaged 11.5 litres of milk per day. He gave 6 grms. of fresh thyroid for ten days, during

which time the average amount of milk rose to 12.55 litres. On the following eight days he gave 8 grms. thyroid and the milk rose to 13.8 litres per diem. The average quantity of milk during the twenty days the animal was under treatment was 13.17 litres, being an increase of 1.67 litres per day.

Lange took nine hens eighteen months old and gave one of them from 10 to 30 grms. of thyroid daily. During the following twenty-eight days the eight hens laid forty-two eggs, or an average of 5.25 eggs, while the hen receiving thyroid laid during the same period sixteen eggs; the



FIG. 15.—Aorta of thyroidectomized sheep showing atheroma.  
(v. Eiselsberg.)

weight of the eggs also increased 10 grms. Lange had previously observed that a thyroidectomized hen laid an egg with a very thin shell weighing only 5 grms.

Metabolism experiments have been made during the administration of fresh thyroid gland, thyroid sicca and thyroidin on healthy subjects, in myxedema, in Basedow's disease, in obesity and in thyroidectomized animals, which give practically the same results. In thyroidectomized animals without thyroid feeding there is a greatly increased elimination of nitrogen and a decreased elimination of phosphorus, the latter rising on the administration of thyroid. Roos kept a dog under observation for two months, estimating the elimination of nitrogen, sodium chlorid and phosphoric acid. He then administered 3.0

grms. and later 6.0 grms. thyroid sicca daily. There was an increased elimination of nitrogen, sodium chlorid and phosphoric acid. He then removed the thyroids and continued the administration of the thyroid sicca, the nitrogen and sodium chlorid elimination was further increased, but the phosphoric acid was diminished. The nitrogen elimination in the unoperated animal rose from 3.04 to 3.8 and from 3.4 to 4.15 and in the operated animal from 3.61 to 5.35. Magnus Levy found that the amount of oxygen utilized by a subject at rest was 3.1 to 5.36 ccm., while in the obese it was only 2.82 (v. Noorden found 2.64). By the administration of thyroid he could raise the O used from 2.26 to 2.36 on the fifteenth day and to 2.55 on the nineteenth day, the loss of weight in the nineteen days being 4 kg. Theile and Nehrung raised the O from 2.87 to 3.43, or 20 per cent; v. Noorden raised the O used 21 per cent, which lasted fourteen days after the thyroid feeding was suspended. Magnus Levy treated a myxedematous patient with thyroid tablets, thyroantitoxin and iodothyrim. With the tablets the patient lost weight from 42 to 39.2 kg., the pulse rose from 60 to 120, temperature from 36.2 to 37.5, the O used from 1.22 to 2.15, the respiration quotient sank from 0.85 to 0.71. With Fraenkel's antitoxin the amount of O used was not increased nor did the pulse rate increase, the body weight did not fall but increased 1 kg. The iodothyrim produced about the same effect as the tablets, the O rose from 1.3 to 1.98, the respiration quotient fell from 0.83 to 0.74, the pulse rate rose from 60 to 100, the body weight fell from 44.2 to 41.9 kg. Stüve found the O used increased in a healthy subject by the administration of thyroid tablets 20 to 23 per cent, while the increase of CO<sub>2</sub> eliminated was somewhat less. Voit arrived at the same conclusions.

Venehren experimented with three normal young men, giving 0.1 to 0.3 iodothyrim per diem and found no change

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in the nitrogen elimination, but in two older subjects there was a marked increase. Dennig found that the nitrogen elimination was increased on the administration of thyroid sicca. Blubtreu and Wendelstaat, in a metabolism experiment on the latter, found that by taking three to four tablets, equal to about 2 grains thyroid sicca each, he lost 3 kg. in weight and 15.97 nitrogen, equal to 500 grms. muscle substance, therefore 16 per cent of the loss of weight was due to loss of muscle substance. Scholz found that by taking three tablets daily his case lost no weight. Before taking the tablets the elimination showed a nitrogen retention  $+3.7567$ , while taking the tablets the nitrogen retention was reduced to  $+2.6399$ . Richter found in the period before administration of the thyroid an N retention  $+4.95$ , during the experimental period  $+3.22$ , and during the after period  $+4.0$ . Gluzinski and Lemberger obtained about the same results by the administration of tablets, but on giving the fresh gland the retention N of  $+2.1$  was reduced to  $-1.48$ , showing that while the subject lost 1 kg. weight he lost 6.24 grms. N, equal to 200 grms. muscle substance, or 20 per cent of the total loss was, therefore, muscle substance. Richter, in order to see if it were possible to reduce the weight without loss of nitrogen, put a subject on a diet containing 20.07 N and equal to 2988 calories, or 40 calories per kg. of body weight. He gave ten, fifteen and twenty thyroid tablets two days each. The subject lost 2 kg. in five days with a nitrogen retention of  $+12.89$ , showing that under sufficiently nitrogenous diet it is possible to reduce weight without loss of muscle substance. In this case the only change noted in the urine was an increase of xanthin elimination.

Schörndorff, in a most elaborate and carefully conducted metabolism experiment on a dog 25 kg. weight in nitrogen equilibrium, found that on the administration of

thyroid the elimination of nitrogen was increased during the first eight days by 1.59 grms. per diem. The elimination then sank to equilibrium, then rose to slight minus and then again fell to equilibrium. The total nitrogen taken was 729.13, eliminated 731.96 equal to a loss of 0.1 gm. per diem. He next increased the amount of thyroid in order to see if after the elimination of the fat the increased oxidation would cause increased loss of nitrogen. During twenty-two days the animal received 729.93 N and lost 760.51 N equal to 927.0 grms, muscle substance; the dog had lost in all 2200 grms. weight, and had, therefore, lost 1273.0 grms. fat; this loss was equal to 40.0 grms. muscle substance and 55.0 grms. fat daily. Contrary to other observers he found that as soon as the thyroid feeding ceased the excessive nitrogen elimination ceased, the animal gaining weight rapidly. He concluded that the increased elimination of nitrogen in the first few days of thyroid feeding is due to the elimination of extractive substances, while the fat metabolism really spares the proteid nitrogen. When the body fat has been reduced to a certain point the nitrogen elimination is increased by the oxidation of proteid.

The effect of thyroid feeding upon the metabolism is the result of increased oxidation and consequent loss of weight. The intake of oxygen is increased, the carbon dioxid given off is increased, the nitrogen elimination is increased. In the first few days, probably by the elimination of extractives, it is possible, by proper diet, to prevent any loss of nitrogen, the loss of weight being then due to the oxidation of the fat and loss of water. The chlorid and phosphoric acid elimination are also increased, uric acid elimination is not affected, but a slight increase in the xanthin bodies has been observed, the total quantity of urine is usually increased. There is also quite a perceptible increase of perspiration which, if very marked, may cause the urine to decrease in quantity.

The administration of thyroid in large doses produces a condition known as thyroidismus, resembling in many points the symptoms of Basedow's disease. Exophthalmos has been observed by Notthaft in the case of a patient who took very large doses for obesity. The resemblance to Basedow's disease was so marked that the diagnosis of Basedow's disease was made before the real cause was discovered. The tremors, mental depression, rapid pulse, diagnostic of Basedow's disease, are almost invariably produced by overdoses of thyroid. Ewald gives a detailed account of the symptoms observed in various cases. The pulse rate is increased to 100-120 or higher, palpitation of the heart, stenocardiac attacks, rise in temperature, a feeling of weakness with constriction of the chest, tremors, insomnia, increased diuresis but, if the sweating is very profuse, the twenty-four hours' urine may be reduced to 300 ccm. or less, with increased elimination of nitrogen, chlorids and phosphoric acid, and may contain albumin; the respiration is accelerated, headache and rheumatoid pains occur, eructations, loss of weight and complete anorexia, thirst, dizziness, loss of consciousness, increased flow of saliva, pruritis, urticaria, erythema, eczema; the heart may become so weak and the vessels so dilated that the patient will keep his head below the level of the heart. Sugar has been observed in the urine by Dale, Jones, Ewald, Bennig and others. It occurred in one case at Mount Hope. Levulose and inosite have both been recorded as occurring. The mental symptoms are usually those of depression. The writer took 24 grs. per diem for three days for experimental purposes, and the depression was so great that the experiment could not be continued. In other cases there is a precordial anxiety with an ill-defined but very real fear of impending danger. Maniacal symptoms occur, usually of a melancholic type, and suicidal tendencies may appear.

The action of thyroid feeding on the heart and circulation has been studied by Oliver, Schaefer, Gley, Langlois, Gurnard and Martin. They find that the pulse becomes weak and rapid. Oliver, by means of his hemodynamometer and arteriometer, showed that the blood pressure is very markedly reduced, while the arteries and arterioles are dilated, especially the peripheral vessels, producing the perspiration. Gurnard and Martin showed that, after the vessels had been dilated and the heart weakened by the injection of thyroid extract, they could be rapidly restored to normal by the injection of suprarenal extract.

The blood changes after thyroidectomy are more constant than any other pathological findings and offer an explanation to most of the symptoms produced by the operation. Horsley, Herzen and Rojwitsh found that the blood became more venous, the former showing that the arterial blood might contain less oxygen than was normal in venous blood. Alberti and Tizzoni found that the O in the arterial blood was reduced from 7 to 8 vol. to 8 to 11 vol.; Vassali propounded the theory that the red corpuscles lost their power to combine with oxygen, and found that when he injected the expressed fluid from a gland into the veins of an operated dog, whose venous blood was almost black, after a few hours the blood became normal in color.

As was previously mentioned it has been observed that operated animals react to external temperatures very readily; the formation of  $\text{CO}_2$  is immediately increased on their being brought into the cold, which only takes place after some time in normal animals. This points to a vasomotor disturbance. Schaefer has shown that the intravenous injection of thyroid extract reduces blood pressure, and Oliver that the calibre of the radial artery is increased at the same time. Lewy made a careful examination of the blood in operated animals and found that the specific gravity was always reduced, but that no other very con-

stant changes existed; further, that no relation appeared to exist between the severity of the symptoms and the anemic changes; normally the leucocytes are present in greater proportion in the veins than in the arteries of the gland, and the proportion is greater than that found in the limbs. Formanek and Haskovic found the number of red corpuscles invariably reduced and the leucocytes increased, the total solids and iron were diminished. Ducceschi found that in operated dogs before the commencement of the convulsion the serum albumin increases and the serum globulin decreases, the total proteids vary from the commencement of the convulsions to the death of the animal, the globulin continues to increase, and the serum albumin and total albuminoids decrease as in starvation. Bottazzi finds the same changes as Ducceschi; also that the red corpuscles part with their hemoglobin very readily, lose in specific gravity and that there is an increase in fibrin. Masoin claims to have found a toxin in the blood of operated animals as well as in the urine; Zuntz and Geppert found acid substances in the blood; Gley found that the blood serum of operated animals produced typical symptoms when injected into the blood of normal animals; Edmunds and Baldi on the contrary could obtain no symptoms under the same conditions.

Excess of mucin has been found in the blood of myxedematous patients and in that of operated animals. Haliburton analyzed the blood tissues and organs of a case of myxedema; the tissues were finely minced, weighed and usually kept a day in methyl alcohol, decanted and the tissues treated with lime water or dilute barium hydrate solution, allowed to macerate for a few days, strained, and the mucin precipitated from the filtrate by the addition of weak acetic acid, filtered through a weighed filter, washed with alcohol and ether, dried at 100 degrees C. to a constant weight and weighed.

By this method a number of analyses have been made with varying results.

The skin of the thigh of a still-born child contained 0.96 per cent mucin; the abdominal skin of children from seven weeks to nine years of age 0.39 to 1.02 per cent, with an average 0.766 per cent; skin from the same part in grown people contained 0.11 to 0.64 per cent, with an average of 0.385 per cent; in connective tissue 0.5 per cent; in Achilles tendons 0.298 to 0.77 per cent; in the parotid gland only a trace. In a patient who had suffered for ten years from myxedema Cranston Charles found fifty times more mucin than normal in the skin of the foot. Halleburton found 0.81 to 0.72 per cent, and once 0.012 per cent, average 0.374 per cent; the quantity in the tendons was increased, 1.42 per cent in the heart, 1.65 per cent in the spleen, 2.21 per cent in the lungs, 0.7 per cent in the parotid. In the blood which clotted imperfectly there was no mucin found, neither in the pericardial, peritoneal or cerebro-spinal fluids. Horsley and Halliburton (Brit. Med. Jour., 1885) found that in monkeys, after the extirpation of the gland, mucin was increased in the tissue as shown by the following table:

|                            | <i>Skin.</i> | <i>Tendons.</i> | <i>Muscle.</i> | <i>Parotid.</i> | <i>Sub-maxillary.</i> | <i>Blood.</i> |
|----------------------------|--------------|-----------------|----------------|-----------------|-----------------------|---------------|
| Normal .....               | 0.089        | 0.009           | 0              | 0               | 0                     | 0             |
| 7th day after operation .. | 0.045        | 0.09            | 0              | trace           | 0.016                 | trace         |
| 29th " " ..                | 0.108        | 0.15            | 0              | 0.208           | 1.036                 | trace         |
| 49th " " ..                | 0.23         | 0.24            | trace          | 0.17            | 0.33                  | 0.08          |
| 55th " " ..                | 0.312        | 0.255           | trace          | 0.072           | 0.6                   | 0.35          |

It was also noted that the blood coagulated very slowly, but that the proportions of serum globulin to serum albumin were normal. It was further observed that pigs did not become myxedematous on thyroidectomy and that there is a quantity of mucin in normal pigs' tissue, the skin contained 0.209 per cent, tendons 0.403 per cent, muscle none, parotid trace, submaxillary gland 0.416 per

cent, blood none, pancreas 0.009. In sheep, on whom the operation had no apparent effect until they were turned out in the cold, the urine became thick with mucus when the symptoms appeared. Byrom Bramwell has observed this symptom in patients suffering from myxedema. Halliburton concludes from the above analyses that the percentage of mucin in the tendons of myxedematous patients slightly exceeds normal, but that excess of mucin in the tissues is not pathognomic of the disease. He reports one case in which the mucin was very excessive. Wagner claimed that by the injection of mucin into the vessels of cats he produced tremors and tetanoid spasms resembling those of thyroidectomy.

The pathological findings in thyroidectomized animals are not marked nor constant, and seem to be the result of starvation rather than toxemia. In the nervous system various writers have found a number of lesions but none occur with sufficient regularity or uniformity to permit them to be considered as pathognomic of the condition. In the central nervous system anemia and edema of the brain and hyperemia with extravasations in the spinal cord have been frequently observed. Pisenti found cavities in the lumbar and costal portions of the cord containing only traces of nerve substance, but such cavities are often found in hyperemic conditions of the brain and cord. In the brain substance a condition of encephalitis parenchymatosis, accompanied by swelling of the nerve cells and axis-cylinder; also a small round cell in filtration of the meninges of the upper portion of the cord have been noted by Horsley and Arthoud. Mayon found a neuritis vagi. Langhans and Kopp, examining the peripheral nerves in the acute cachexia of dogs and in the more chronic cases of monkeys, men and cretins, found changes of an inflammatory nature. Although no definite constant change has been observed in the nervous system there can

be no doubt that the symptoms are of central origin. Schiff has shown that the tetanic convulsions ceased on section of the nerve trunks; Lang cut the sciatic nerve in an operated dog and saw the twitching cease in the muscles supplied by the nerve; Horsley and Lang cut the cord at the eighth vertebra and saw the twitching almost cease in the extremities. The motor area of one hemisphere was removed by Horsley in five operated dogs, the twitchings were more marked on the side which was intact. The results of these experiments prove that the disturbances are of central and not peripheral origin.

Zesas and Cr  d   and also Lemke found that the spleen became enlarged after removal of the thyroid, and L  hleln that after the removal of the spleen the thyroid enlarged. Zanda claimed that if the spleen was removed four weeks the thyroid could be removed without causing any symptoms, and argued that the spleen produced toxic substances which it was the function of the thyroid to neutralize. Fano on repeating Zanda's experiments did not confirm his results. Hofmeister, Albertoni, Tizzoni, Gley and de Quervain failed to confirm Zesas and Cr  d  's observations, and found in five cases of men dying of cachexia strumipriva that the spleen was unusually small in four cases and of normal size in one. Lang in over forty experiments failed to show any connection between the spleen and the thyroid.

Gley found that by extirpating portions of the thyroid at different times in rabbits he could produce hypertrophy of the hypophysis cerebri, the weight of the latter being increased from 0.02, the average normal weight, to 0.101 grms. There has been much speculation as to the possibility of the vicarious action of the hypophysis for the thyroid, which was rendered probable by the former occasionally containing iodine, but there has been very little evidence forthcoming in support of the theory.



In operated animals the temperature is usually normal except during the tetanic spasms, when it may rise 2 to 5 degrees C., Herzen on one occasion observing a temperature of 43.4 degrees C., later the temperature falling below normal; it may go as low as 33 degrees C. There is marked susceptibility to cold in operated animals, which is also very evident in myxedematous patients. Munk, Lang and Kocher observed that the patients suffering from cachexia strumipriva were more comfortable in warm rooms, complaining of cold at ordinary temperature. By increasing the external temperature operated animals can be kept alive much longer and the cachexia and tetany reduced to a minimum. Whether the feeling of cold is central in origin or the result of trophic changes of the skin has not been decided.

During the convulsions the respiration is increased, between the attacks it is normal or reduced; the type is normal. The heart's action is increased in volume.

The urine shows no very marked change, it is usually decreased in quantity, of an increased specific gravity and may contain albumin during the convulsions. The toxicity has been found to be increased by Gley and Laulanie, who claim that on the injection of the urine of an operated animal into the veins of an unoperated animal typical symptoms were produced. Alonzo and others have failed to corroborate their results and could find no appreciable difference. The nitrogen and chlorid elimination is increased, while the phosphoric acid is decreased, the proportion of neutral sulphur to total sulphur is also increased. The increased elimination of nitrogen and chlorids is no doubt due to the progressive anemia and consequent starvation, while the decreased phosphoric acid and increased neutral sulphur may be due to decreased oxidation. There is probably some connection between the phosphorous metabolism and the thyroid secretion, as

the effect of congenital absence or early removal of the gland produces an arrest of development, especially of the skeleton, the long bones and vertebræ suffering the most. Hofmeister made exact comparative measurements in animals and found that the growth of the long bones was decreased one-third.

The influence of food on the symptoms of thyroidectomy is marked. Briesacher found that dogs suffered less and could be kept alive longer if fed on well-cooked meat and milk, while if given raw meat or meat extract they succumbed much earlier. On milk diet the animals lived longer or survived in apparently perfect health with only one-third to one-fifth of the gland remaining. Herbivora seem also to suffer less than the carnivora, due presumably to their vegetable diet.

## CHAPTER IV.

### CHEMISTRY OF THE THYROID GLAND.

Since the thyroid has been proved to be a secreting organ and of vital importance to the system, the chemical nature of its secretion has been the subject of most careful research by numbers of physiological chemists, both in Germany and England, their efforts having been directed to the isolation of the active principle. That the gland contained considerable quantities of extractives, viz: xanthin, hypoxanthin, kreatin, kreatinin, paralactic acid, inosite (?), indicating high metabolic activity was early proved, but none of these could be looked upon as the active principle. White and Davis, working on the hypothesis that the active principle was a ferment, obtained a body which had some activity. Gourlay failed to find a ferment which would dissolve mucin, which was considered at that time to be the function of the gland, but he isolated a nucleoalbumin which produced intravascular clotting, and which he claimed existed in the colloid substance. Bubnow extracted three different forms of proteid, one apparently a globulin; Notkin following on the same lines isolated a substance which he believed was the toxic product of metabolism, which underwent decomposition in the gland through the action of an hypothetical enzyme. In 1895 Sigmund Fraenkel isolated a crystalline alkaloid-like body resembling guanidin to which he gave the empirical formula  $C_6H_{11}N_3O_5$ . Drechsel later described a body identical with that of Fraenkel and another similar to it. Fraenkel's thyroantitoxin was a hygroscopic crystalline substance, soluble in water and alcohol, neutral to slight alkalinity and gave the alkaloid

reactions. Injected into animals it failed to produce a fall in blood pressure but increased the pulse rate; administered to thyroidectomized animals it caused some improvement in their condition. Fraenkel's observations have not, however, been confirmed; the epoch-making discovery of Professor Baumann of Freiburg, in 1896, of a body containing iodine in organic combination in the thyroid of man and of many animals, possessing the physiological characteristics of the gland, prevented any further experiments in that line. Baumann describes the substance he isolated, which he named "thyroidin," as a brownish amorphous compound which decomposed on heating, giving off the odor of pyridine, it is insoluble in water, sparingly soluble in alcohol but dissolves readily in dilute alkalis, being precipitated by acids, it gave no proteid reactions, and constantly contained phosphorus; he obtained 9.3 per cent iodine in crystalline form from this substance. Baumann was unable to complete his work, owing to his lamented death in 1897, when physiological chemistry lost one of its ablest disciples. His method for the isolation of the thyroidin consisted in digesting the gland for several hours with a 10 per cent mineral acid on a sandbath with a return condenser and extracting the residue with 90 per cent alcohol. He proved that the substance was iodine in proteid combination, and he named it thyroid albumin. Drechsel and Baumann found that the iodine-containing proteid could be dissolved in normal salt solution, which solution he diluted with fifteen volumes of distilled water, passed carbon dioxide through it, obtaining a precipitate of a globulin containing iodine, he added acetic acid to the filtrate and boiled, securing a precipitate of albumin which also contained iodine, and therefore concluded that there were two iodine-containing proteids in the gland, a globulin and an albumin.

Oswald extracted 99.5 grms. of human thyroid which contained 21.92 mg. iodine ten times with normal salt solution, and obtained 17.26 mg. I in solution, being 78.7 per cent of the total I; Lambach obtained 97.8 per cent in solution; in neither case was there any iodine in inorganic combination.

Oswald then proceeded by Pick's method to separate the albumins and found that the precipitation commenced at 0.26 and continued up to 0.44 saturation, so that at 0.5 saturation one proteid was completely precipitated, in the filtrate precipitation begun at 0.64 and continued up to 0.82 saturation when the filtrate contained no proteid. He found that the first precipitate contained iodine but no phosphorus, while the second precipitate contained no iodine but contained phosphorus, proving that the separation of the proteids was complete. The first precipitate was dissolved in water, filtered and again half saturated with ammonium sulphate. This precipitate was dialyzed till free from ammonium sulphate, redissolved in alcohol (95 per cent), filtered and the precipitate dried. An easier method which dispenses with the tedious dialyzing is to dissolve the precipitate from the half-saturated ammonium sulphate solution in water and precipitate with dilute acetic acid, filter, dissolve the precipitate in 0.1 per cent sodium hydrate, precipitate with acetic acid, washing the precipitate with water acidulated with acetic acid.

The precipitate is only very slightly soluble in water, but is more easily dissolved by the addition of neutral salts, is very soluble in dilute alkalis, is precipitated by slight acidulation with acetic or hydrochloric acids. Saturation with sodium chlorid produces only a slight cloudiness, saturation with magnesium sulphate and half saturation with ammonium sulphate give complete precipitation. These reactions are those of the globulins and Oswald designates the iodine-containing globulin as thyroglobulin.

Myosin is precipitated from its solution in neutral salts by acids and gives the other globulin reactions, egg and serum globulin are not thus precipitated. This substance is not pseudomucin, as is often stated, as pseudomucin is not precipitated by acids.

Thyroglobulin is precipitated by sulphuric acid but is not soluble in excess. It is also precipitated by phosphotungstic acid, phosphomolybdic acid, ferrocyanid of potassium, acetic acid, iodo-mercuric potash, trichloroacetic acid and by copper sulphate. It gives the color reactions for proteids, the biuret reaction, Millon's reaction, Adamkiewicz's reaction, Mollisch reaction and the xanthoproteic reaction.

The salt free solution becomes cloudy on heating but does not coagulate, on the addition of 10 per cent magnesium sulphate it coagulates at 65 degrees C.; it contains sulphur which combines with lead. From the strong result of Mollisch's reaction it may be assumed that it contains a large carbohydrate group in the molecule; after boiling for two hours with 5 per cent solution of hydrochloric acid the solution gives the red reaction with  $\alpha$ -naphthol and sulphuric acid, and also reduces Fehling's solution and ammonia silver oxid, while it fails to give the typical phloroglucin and hydrochloric acid reaction, it gives a brown color with this test, showing that pentose is not present; it forms osazone with a melting point of 100 degrees C. with phenylhydrazin (Hutchinson failed to obtain a reducing substance from sheeps' thyroid and Reinbach from the colloid of calves' thyroids). In making the elementary analysis of his thyroglobulin Oswald used the Fresenius method for estimating the iodine, having found that the estimation as silver iodid gave too high results, owing to the precipitation of silver chlorid. As the estimation of the iodine in the preparations on the market is of value as an indication of their activity the

method is here given: A weighed quantity of the substance to be tested is placed in a nickel or porcelain crucible with a little water and pure sodium hydrate, evaporated to dryness, a little potassium nitrate added, then incinerated, the residue dissolved in hot water, filtered, and the filtrate placed in a well-stoppered bottle with about 10 ccm. of carbon disulphid, acidulated with sulphuric acid and nitrous acid, the solution is extracted several times with carbon disulphid, the iodine is dissolved in the carbon disulphid which is washed two or three times with water. The titration is then carried out with a solution of hyposulphite of soda standardized against a solution of potassium iodid of known strength.

When thyroglobulin is submitted to pepsin digestion for four weeks a gray brown flocculent precipitate remains, which contains iodine, gives the xanthoproteic reaction but neither the biuret, Millon's nor Mollisch's reactions, and is precipitated from its solution with phosphotungstic acid. Hutchinson, by digesting thyroglobulin prepared by his method, obtained a substance which gave no biuret reaction but contained 0.8 per cent phosphorus, showing that the residue contained nuclealbumin as well as thyroiodine. Oswald separated the albumoses and peptones in the solution from the pepsin digestion by the Pick method and found that the protalbumose and deuteralbumose contained iodine in quantity and that the peptone B contained a small quantity, while the heteroalbumose and peptone A contained only faint traces, which were probably due to impurities.

The digestion of thyroglobulin with trypsin for four weeks resulted in a clear solution, which only gave faint cloudiness with ammonium sulphate, acetic acid produced no precipitate, showing that the iodine thyroglobulin was completely broken up, though the solution contained iodine in organic combination. On concentration of the solution

tyrosin crystals were found and on further concentration leucin. This decomposition by trypsin digestion and the iodine remaining in organic combination shows that the iodine is not combined in the tyrosin group of the thyroglobulin molecule.

Thyroglobulin treated with 10 per cent sulphuric acid on the sandbath with a return condenser is split up, leaving a brown flocculent residue and a brown colored solution, on filtering and washing till the wash water is free from sulphuric acid, extracting with boiling alcohol till the latter is no longer discolored, the alcohol solution evaporated to dryness and dried to a constant weight leaves a brownish powder, which is insoluble in water or acids but is easily soluble in alkali. It gives neither the biuret, Millon's or Mollisch's reactions but gives the xanthoproteic reaction, contains much iodine and corresponds with Baumann's thyroïdin. Thyroglobulin is split up with concentrated acids and with barium hydrate.

Oswald proved the physiological effect of the thyroglobulin on the metabolism of animals, finding that it increased the elimination of nitrogen.

The second proteid separated from the normal salt solution of the gland, and which contained no iodine, contained 0.16 per cent phosphorus, coagulated in a 10 per cent solution of magnesium sulphate at 73 degrees C. with  $\alpha$ -naphthol and sulphuric acid it gave a red color, with phloroglucin and hydrochloric acid a brown color, showing that the carbohydrate group is not probably a pentose; it also contained xanthin bases and is, therefore, a nucleoproteid; further, on being given to animals it failed to increase the elimination of nitrogen.

Oswald made an elementary analysis of the thyroglobulin from the glands of man, pigs, sheep, oxen and calves:



|                | <i>Man.</i> | <i>Swine.</i> | <i>Sheep.</i> | <i>Oxen.</i> | <i>Calves</i><br><i>Goitrous.</i> | <i>Calves</i><br><i>Normal.</i> |
|----------------|-------------|---------------|---------------|--------------|-----------------------------------|---------------------------------|
| Carbon .....   | 51.85       | 52.21         | 52.32         | 52.45        | 52.28                             |                                 |
| Hydrogen ..... | 6.88        | 6.83          | 7.02          | 6.93         | 7.04                              |                                 |
| Nitrogen ..... | 15.49       | 16.59         | 15.9          | 15.92        | 15.99                             |                                 |
| Iodin .....    | 0.34        | 0.46          | 0.39          | 0.86         |                                   | 0.56                            |
| Sulphur .....  | 1.87        | 1.86          | 1.95          | 1.83         | 2.00                              |                                 |
| Oxygen .....   | (23.57)     | (22.15)       | (22.42)       | (22.01)      | (21.61)                           |                                 |

Baldoni analyzed the thyroids of calves, sheep, pigs, horses and oxen obtained from the slaughter houses in Rome:

|             | <i>Albumin.</i> | <i>Globulin.</i> | <i>Nucleoproteid.</i> | <i>I in dry</i><br><i>Gland.</i> | <i>I in</i><br><i>Globulin.</i> |
|-------------|-----------------|------------------|-----------------------|----------------------------------|---------------------------------|
| Calf .....  | 70.58           | 61.41            | 4.15                  | 0.842                            | 1.33                            |
| Sheep ..... | 63.16           | 53.58            | 3.69                  | 0.652                            | 1.16                            |
| Horse ..... | 70.6            | 58.56            | 4.45                  | 0.677                            | 1.1                             |
| Ox .....    | 68.17           | 58.49            | 3.43                  | 0.615                            | 1.01                            |
| Pig .....   | 64.21           | 50.46            | 3.55                  | 0.311                            | 0.58                            |

These analyses show that the constituents of the thyroglobulin in all the animals examined are almost proportionately the same, while the iodine may vary from 0.0 to 0.86, as in calves. The calves' glands which contained no I were from Zurich and were very large, being from 60 to 300 grms. in weight; they were not colloid goitres but hypertrophied glands in which no colloid could be seen. The glands containing 0.36 iodine were from Paris, their average weight being from 15 to 20 grms., showing a considerable amount of colloid. These analyses of calves' glands are of special interest, as they show that the goitrous glands contain a thyroglobulin which has the same elementary analysis as in oxen but contains no iodine. The thyroglobulin containing no iodine was proved to be physiologically inert by Lyon and Oswald, which shows that the physiological activity of the thyroglobulin depends on its containing iodine in the molecule.

Oswald made the following analyses of the thyroglobulin of human glands:

|                | <i>From Colloid Goitres<br/>from</i> |                |      | <i>Basedow's<br/>Disease.</i> |       | <i>Glands Rich in Colloid<br/>from Hamburg.</i> | <i>Glands of Children in<br/>Zurich.</i> | <i>Normal Glands from<br/>Hamburg.</i> | <i>From a Colloid Goitre<br/>from Zurich after ad-<br/>ministration of Po-<br/>tassium Iodid.</i> |
|----------------|--------------------------------------|----------------|------|-------------------------------|-------|---|--|--|---|
|                | <i>Basel.</i>                        | <i>Zurich.</i> |      |                               |       |   |  |  |   |
| Carbon .....   | 52.02                                | 51.77          |      |                               |       | 51.82   |  | 51.85                                  |   |
| Hydrogen ..... | 6.91                                 | 6.71           |      |                               |       | 7.05  |  | 6.88                                   |   |
| Nitrogen ..... | 15.32                                | 15.09          |      |                               |       | 15.46   |  | 15.40                                  |   |
| Iodin .....    | 0.07                                 | 0.19           | 0.07 |                               | 0.19  | 0.18  | 0.34                                     | 0.51                                   |   |
| Sulphur .....  | 1.93                                 | 1.93           |      |                               | 1.83  |   | 1.87                                     |  |   |
| Oxygen .....   | 23.75                                | 24.31          |      |                               | 23.65 |   | 23.57                                    |  |   |

These analyses show that the elementary composition of the thyroglobulin is the same in men and in animals, with the exception of the iodine, and that the latter is variable both in animals and in men. They further show that the thyroglobulin in goitrous glands is less than in the normal gland; that the glands rich in colloid contain about twice as much iodine as normal glands; that the relative iodine of the thyroglobulin of the glands rich in colloid and in colloid goitres is smaller while the absolute iodine contents of the whole gland is higher. The fact that in the thyroglobulin from a case of Basedow's disease where the gland was extirpated during life, the percentage of iodine is the same as in the colloid goitres from Basel is of particular interest; also that the gland of the patient to whom potassium iodide had been administered, which was an enlarged gland rich in colloid, contained a much greater quantity of iodine than the other Zurich glands and much more than the normal glands from Hamburg, which seems to prove that the thyroglobulin of the gland is capable of combining with the iodine administered by the mouth and suggests the possibility that the symptoms of iodism and of poisoning with iodoform may be the result of an increased formation and consequent absorption of thyroglobulin containing iodine. Another point of importance suggests itself from the analyses that there is in some

glands, if not in all, a quantity of thyroglobulin containing no iodine, which argues in favor of the theory that the thyroglobulin is secreted iodine free, and that the iodine enters into combination with the previously formed thyroglobulin. Again, has the thyroglobulin any physiological function when not combined with iodine?

The question arises, Does the thyroid contain iodine thyroglobulin only when colloid is present or at least visible under the microscope, and if not visible under the microscope is iodine absent from the gland? If iodine is absent from a gland in which no colloid can be found it follows that the thyroglobulin must be first excreted from the cells before it combines with the iodine and becomes active. The results of a number of analyses have apparently proved that the amount of iodine bears a direct relation to the amount of colloid substance. In a gland which contained but little colloid the analysis showed that the relation of iodine thyroglobulin to the total weight of the gland was 1 to 10, while in another, which was full of colloid, the relation was 2 to 3; this also proves that by far the greatest proportion of the colloid substance is thyroglobulin; in fact so small is the proportion of nucleoprotein that it is possibly only the product of the nuclei of the cells which rupture into the follicles of the gland.

The amount of the total iodine in the glands varies within wide limits. Roos analyzed many glands and found that, generally speaking, the glands of the true carnivora very seldom contain iodine, graminivorous animals always contain it, rodents usually have it, also omnivorous animals, cats have very little. The quantity of iodine in the glands of man varies very much according to locality. Weis found the average of glands in Silesia averaged 4.04, in Breslau 3.8 mg. Oswald found that glands from Geneva averaged 9.32 mg.; Lausanne 7.07 mg.; Basel, 6.48 mg.; Zurich, 10.27 mg.; Bern, 13.04 mg. Baumann found that

in Freiburg they averaged 2.5 mg.; Hamburg, 3.8 mg.; Berlin, 6.6 mg. Rosetzki found in Styria an average of 3.21 mg.; Iolen in Sweden 3.08 mg.; Wells in Chicago 10.79 mg. During fetal life and early childhood iodine is absent or only present in traces. Wells found in Chicago as much as 0.076 mg. in a child four weeks old, 0.532 mg. at four years old and 3.19 at seven years of age. Wells, in a number of analyses from Chicago, tabulates the following:

| <i>Sex.</i> | <i>Age.</i> | <i>Cause of Death.</i> | <i>Weight of Gland.</i> | <i>Iodine Per Gram in Mg.</i> | <i>Total Iodine in Mg.</i> |
|-------------|-------------|------------------------|-------------------------|-------------------------------|----------------------------|
| Female....  | term        |                        | 0.135                   | trace                         | trace*                     |
| Male.....   | term        |                        | 0.465                   | trace                         | trace*                     |
| Female....  | term        |                        | 0.73                    | trace                         | trace*                     |
| Male.....   | 4 weeks     | Lobular pneumonia      | 0.68                    | 0.11                          | 0.076                      |
| Male.....   | 4 weeks     | Meningitis             | 0.18                    | 0.42                          | 0.076                      |
| Male.....   | 4 years     | Diphtheria             | 0.58                    | 0.92                          | 0.532                      |
| Female....  | 7 "         | Phthisis               | 1.61                    | 1.98                          | 3.19                       |
| Male.....   | 45 "        | Chronic nephritis      | 2.6                     | 2.86                          | 7.47                       |
| Male.....   | 60 "        | Brain tumor            | 4.39                    | 2.64                          | 11.75                      |
| Male.....   | 60 "        | Tubercular peritonitis | 2.59                    | 1.67                          | 4.33                       |
| Male.....   | 35 "        | Pneumonia              | 3.88                    | 2.58                          | 10.00                      |
| Male.....   | 35 "        | Peritonitis            | 3.84                    | 2.66                          | 10.21                      |
| Male.....   | 45 "        | Pneumonia              | 10.59                   | 0.99                          | 10.47                      |
| Male.....   | 44 "        | Pneumonia              | 6.33                    | 1.52                          | 9.62                       |
| Male.....   | 28 "        | Endocarditis           | 3.71                    | 2.74                          | 10.17                      |

| <i>Sex.</i> | <i>Age.</i> | <i>Cause of Death.</i>  | <i>Weight of Gland.</i> | <i>Iodine Per Gram in Mg.</i> | <i>Total Iodine in Mg.</i> |
|-------------|-------------|-------------------------|-------------------------|-------------------------------|----------------------------|
| Male.....   | 26 years    | Liver abscess           | 4.47                    | 2.58                          | 11.53                      |
| Male.....   | 46 "        | Chronic nephritis       | 5.16                    | 1.82                          | 9.41                       |
| Male.....   | 30 "        | Appendicitis            | 5.79                    | 1.98                          | 11.46                      |
| Male.....   | 28 "        | Pulmonary tuberculosis  | 4.88                    | 2.28                          | 11.15                      |
| Male.....   | 40 "        | Carcinoma of stomach    | 3.77                    | 1.98                          | 7.46                       |
| Male.....   | 30 "        | Multiple Endotheliomata | 9.68                    | 1.82                          | 17.62                      |
| Male.....   | 35 "        | Acute nephritis         | 6.66                    | 1.52                          | 10.12                      |
| Male.....   | 41 "        | Chronic nephritis       | 6.53                    | 1.98                          | 12.83                      |
| Female....  | 25 "        | Syphilitic myelitis     | 5.44                    | 1.82                          | 9.9                        |
| Male.....   | 26 "        | Pneumonia               | 9.01                    | 1.98                          | 17.84                      |
| Male.....   | 66 "        | Meningitis              | 5.24                    | 1.52                          | 7.96                       |
| Male.....   | 65 "        | Pneumonia               | 4.10                    | 1.22                          | 5.0                        |

He also gives the following from Boston and New York:

\* Not over 0.03 mgrs.

| <i>Sex.</i> | <i>Age.</i> | <i>Cause of Death.</i> | <i>Weight of Gland.</i> | <i>Iodin Per Gram in Mg.</i> | <i>Total Iodin in Mg.</i> |
|-------------|-------------|------------------------|-------------------------|------------------------------|---------------------------|
| Male.....   | 30 years    | Phosphorous poisoning  | 5.48                    | 2.36                         | 12.93                     |
| Male.....   | 45 "        | Suffocation            | 3.65                    | 4.94                         | 18.03                     |
| Female....  | 40 "        | Pneumonia              | 4.43                    | 1.9                          | 8.42                      |
| Female....  | 25 "        | Appendicitis           | 3.84                    | 2.58                         | 9.13                      |
| Male.....   | 55 "        | Pneumonia              | 4.77                    | 1.9                          | 9.06                      |
| Female....  | 40 "        | Pneumonia              | 3.54                    | 4.56                         | 16.14                     |
| Female....  | 60 "        | Chronic nephritis      | 3.81                    | 2.13                         | 8.12                      |
| Male.....   | 60 "        | Pneumonia              | 3.47                    | 1.44                         | 6.86                      |
| Female....  | 35 "        | Mitral stenosis        | 6.37                    | 2.20                         | 14.01                     |
| Male.....   | 47 "        | Poisoning              | 3.44                    | 2.51                         | 8.63                      |
| Male.....   | 25 "        | Pneumonia              | 4.65                    | 2.74                         | 12.74                     |
| Male.....   | 55 "        | Meningitis             | 6.18                    | 2.66                         | 16.44                     |

Comparing his analyses with those of Baumann and others he concludes that the amount of iodine is inversely proportioned to the amount of goitre in the district; and that the usually accepted theory that the iodine is decreased in chronic diseases is not according to the results of his analyses, but that in old age the amount of iodine is much below the average.

F. Blum claims that iodothyron has an inconstant quantity of sulphur in the molecule and that the molecule is not saturated with iodine. He considers iodothyron to be an unsaturated iodine toxalbumin, that the toxin is the iodothyron without the iodine and that it renders harmless substances which are being continually formed in the organism by means of the iodine. In support of this view Roos shows that the saturation of the iodothyron molecule with iodine renders it inert, and he finds that the artificially produced iodoalbumins give the same reactions as the thyroid albumins, and will also produce iodine compounds similar to but not identical with iodothyron, which he claims proves that iodothyron is a decomposition product from a thyroid iodoalbumin; he also states that after the administration of iodide other organs besides the thyroid form iodoalbumins, but the thyroid the most readily. He concludes that the hypothetical metabolic poison combines

with the secretions of the thyroid, the most active of which is the one containing iodine, and that the toxin plus the iodoalbumin is the toxalbumin of the thyroid.

Fraenkel extracted the dried gland with acetic acid when the proteids were precipitated and found the precipitate inactive, while the filtrate was active in obesity. He concentrated the filtrate, treated with alcohol and precipitated with ether or acetone, obtaining a crystalline alkaloid which increased the pulse rate when injected into the veins of a morphinized dog from 56 to 140, and decreased the convulsions but did not save the life of thyroidectomized cats.

Lanz states that thyroid sicca from swine, sheep or calves were equally as good, and that 10.0 grms. of fresh gland per day was sufficient to keep a thyroidectomized dog alive. Wormser was unable to keep operated dogs alive with any preparation except thyroid sicca. Baumann and Goldman were able to reduce the tetanic attacks in operated animals with from 2 to 6 grms. thyroidin per diem and brought the tetanic convulsions to an end with 65.0 grms., but had to repeat the dose. Wormser found that the precipitate from normal salt solution with acetic acid did not prevent attacks or death in operated animals; that the proteids with dissolved thyroidin were inactive; that synthetically prepared iodine containing proteids were inactive.

Hutchinson published his work on the chemistry of the thyroid in 1896 and arrived at nearly the same conclusions as Oswald. His method was to treat the fresh gland with a one-tenth per cent solution of sodium hydrate and to precipitate with acetic acid.

E. Lépine examined the thyroid for oxidase and found an indirect oxidase which gave the blue reaction with tincture guaiacum upon the addition of hydrogen dioxide. The presence of this indirect oxidase in the thyroid is of

great importance, as it may account for the increased oxidation in the system from the administration of the gland.

Gautier claims to have found arsenic in the glands of dogs, swine, sheep and man. The question as to whether this is ingested with the food and is merely as it were an impurity or whether arsenic is necessary for the normal functionation of the gland has not been decided. Stein has found that many of the garden vegetables, such as cabbage, potatoes, turnips, contain arsenic.

Paderi and Baldi have both found traces of bromin in the glands of dogs. If this should be confirmed and it should also be proved that bromin was necessary for the systemic metabolism, every member of the halogen group will have been shown to be a normal constituent of the body.

Conrad and Marchetti performed complete thyroparathyroidectomy on dogs and fed them with dibromostearic acid. In some cases it was administered before the operation, in one it was continued after the operation, and in another the feeding was entirely postoperative when the symptoms were at their height. This treatment apparently caused the attenuation and final disappearance of the symptoms for a more or less prolonged period. Not only was this true of the nervous and muscular excitation and depression but also of the cachexia, the animals living in a condition of apparent health. These dogs having undergone the same operation, were fed with chloriodostearic acid and two with di-iodostearic acid. In the former the results were preëminently satisfactory, in the latter hypodermic administration only gave good results. The authors believe that the salutary influence of the halogens studied upon operated animals are to be attributed to the effect of the bromin and iodin, and to a more complex physiological action representing within certain limits the functions of the thyroparathyroid tissues.

There seems to be no doubt that in Oswald's iodine containing thyroglobulin we have at least the chief, if not the only, active principle of the gland, and it is certain that iodine in the molecule is also necessary for perfect functioning. That thyroglobulin without iodine in the molecule is physiological is probable, but to what extent is not at present known. The phosphorus containing proteid, which has been classed as a nucleoproteid, though small in quantity, may have some physiological activity, as the gland has some connection with the phosphorous metabolism and the calcification of the bones.

There are three distinct theories as to the function of the thyroid gland; that it is a secreting organ which is necessary for the metabolism or for the nourishment of the system; that it secretes an antitoxin for the poisonous products of metabolism; that there is a form of digestion in the gland whereby the toxic substances of metabolism are converted into useful and necessary substances for the organism by the action of an enzyme, and that in the absence of these necessary substances the symptoms are produced.

The advocate of the latter theory is Notkin, who found that by the injection of 2.0 grms. per kg. of the acetic acid precipitate from a normal salt solution extract of the fresh gland into the veins or abdominal cavity of a partially thyroidectomized dog he produced death with symptoms of general paralysis, while repeated small doses produce a cachexia resembling myxedema. His theory is that there are two substances being continually produced in the body as a result of metabolism, one a toxin which produces tetanic symptoms if allowed to accumulate, the other is a peculiar proteid substance, which, if similarly allowed to accumulate, produces the cachectic condition known as myxedema. According to this theory it is the function of the thyroid to antagonize these substances.

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The first substance is destroyed by the action of Fraenkel's thyroantitoxin, which is basic in nature and unites with and neutralizes the toxin, the convulsions in operated animals are due to an arrest in the supply of the antitoxin. The second substance, which produces myxedema, is conveyed to the thyroid by the blood and thus split up by a ferment into two constituents, one of which is of the nature of a carbohydrate and is set free, the other is a proteid which unites with an organic iodine compound, rendering it harmless. He denies that the iodine compound is able to prevent the convulsions which follow thyroidectomy, and he believes that it can only cure myxedema when there is some thyroid tissue left to utilize it, and make it unite with the proteid substance, which he claims produces myxedema. This complicated and ingenious theory has several objections: one is that it has been shown that the colloid substance without the antitoxin will prevent or mitigate the convulsions; that the presence of an enzyme in the thyroid is purely hypothetical, there being no experimental evidence of the existence of such a substance, and further, if this theory were correct thyroid feeding should make myxedematous patients worse instead of which it is curative.

The antitoxic theory has been advocated by Ewald, Blum and others, being expressed in two ways, that the antitoxin in the gland seizes on the toxin in the blood, acting upon it in the gland itself, and that it is only the neutralized toxin which passes into the blood stream, thus acting in an analogous manner to the bodies of Langerhans in the pancreas. The other theory is the result of the doctrine of autointoxication, so ably brought forward by Albu, by which he attempts to prove that almost all diseases result from this cause; it presumes that constantly during life the normal metabolism is producing lower chemical forms derived from proteid, which accu-

mulating through failure of excretion or neutralization, poison the system, producing various symptoms. The antitoxin theory of the function of the gland presumes that the active principle of the gland neutralizes or decomposes one or more of these toxins into innocuous substances. It is probable that the decreased oxidation resulting from thyroid insufficiency will prevent the perfect metabolism of the body proteids and if these imperfectly oxidized substances are toxic, then by increasing the oxidation they will be destroyed and in this sense the thyroid may be considered antitoxic in its functions. So far the advocates of this theory have failed to isolate or detect these toxins in the blood or in the urine of thyroidectomized animals. As previously mentioned one or two observers claim to have produced typical symptoms by injecting the serum or urine of operated dogs into healthy animals, but their results have not been confirmed. Recently Basedow's disease is said to have been successfully treated by injecting the serum from a thyroidectomized goat into the patient but even if this success is confirmed it does not prove the theory. In opposition to the antitoxic theory are arrayed nearly all the facts of experimental and chemical physiology, the extract of the gland reduces blood pressure, increases the amount of oxygen absorbed; increases the elimination of carbon dioxide, increases the nitrogen elimination by the urine and increases temperature in normal subjects, besides producing a variety of symptoms which are hardly compatible with the theory. Again, in cretinism and myxedema, two diseases which are admittedly due to thyroid insufficiency, the patients arrive at a certain stage and remain stationary, while if the diseases were due to the accumulation of toxins they would be progressive. All the metabolism experiments show that the action of the gland substance is in close relationship with the general metabolism and

it has the direct effect of increasing the assimilation of oxygen. How important oxygen is to the systemic functions is self-evident; even a small excess of carbon dioxide in the atmosphere of a room will, by reducing the amount of oxygen inhaled, produce discomfort. The proper distribution of oxygen to the various organs and tissues is the *sine qua non* of life and if this supply is decreased the cell nutrition and activity must be impaired. The special connection of the thyroid with the organs of generation cannot be explained by the theory that its function is antitoxic.

Of the function of the parathyroids little is known at present; they appear to be connected with the thyroid and perhaps to have some special relation to the nervous system.

From its origin and mode of evolution it would seem that the thyroid is to be considered as associated with the respiratory gaseous exchange of the blood and tissues, the phenomena following its destruction by disease or experiment are to be interpreted as a disturbance of the gaseous metabolism, especially with the malassimilation of oxygen by the body tissues, to which are probably correlated the subnormal temperature, twitchings, loss of fat, and the languor and weakness of brain and muscle tissue associated with the condition. It is also probable that there is some connection between the thyroid and the phosphorous metabolism.

## CHAPTER V.

### GOITRE.

Goitre, struma—*Goitre*, French; *kropf*, German; *gozzo*, Italian; *lobanillo*, Spanish; *wen*, *Derbyneck*, English.

The term goitre was first used by the early writers for the enlargement of any organ or gland which was so evident as to be a visible deformity, but has in recent years been restricted to enlargement of the thyroid gland. Struma is an abbreviation from *struere* and *ruma* defined as *struere rumam seu propendentem de collo mammam*. It was also termed gutter turgidum or bronchocele.

It is remarkable that the ancient writers on medicine have left so few records of so evident a deformity as goitre. Plinius, Vituw and Ulpian mention the disease, looking upon it as a divine punishment. The same view seems to have existed in the middle ages, as on many of the old churches where goitre is endemic the griffins and devils are represented with goitres as if it were a mark of depravity. Marco Polo, writing in the thirteenth century, mentions its existence in the highlands of Central Asia.

Paracelsus, in the fifteenth century, describes the disease as occurring in the Tyrol, pointing out its association and probable connection with cretinism. Malcarné, of Turin, published in 1789 a series of scientific observations followed in 1800 by Fodéré. From this time the literature has increased until it has become so voluminous that in 1893 the catalogue of the Surgeon-General's Library at Washington contained no less than 1857 references to articles on the thyroid gland and its diseases.

Goitre occurs as an endemic, epidemic and sporadic disease. The endemic form occurs in more or less circum-

scribed areas in both hemispheres, being always associated with cretinism. To what extent the disease exists in affected districts can be gathered from the government military statistics. In Switzerland, between the years 1875 and 1881, no less than 12,277 men were rejected on account of the deformity; in Italy, between 1859 and 1864, 301 out of every 10,000 inhabitants were rejected, of whom 209 were cretins and 92 goitrous; in 1883, in Piedmont, there were 154 cretins for every 10,000 inhabitants; in Lombardy, 205, and in Venice 23. The total population of these three provinces was 9,565,000, of whom 12,882 were cretins and 128,730 goitrous.

A remarkable feature of the disease is its periodicity, at one time declining in a particular neighborhood and then again increasing, or it may suddenly appear in a district where it was previously unknown. Denny states that when the French first settled at Pittsburg goitre was unknown, and that in 1798 it had become so prevalent that out of 1500 inhabitants 150 were goitrous, after 1806 it began to decline.

There are many cases on record where an epidemic of acute goitre has occurred in places where it was previously unknown. In 1877, in the barracks at Belfort, Vigny and Richard observed 900 cases among 5300 men. In 1889 Angieras saw 18 cases in a wing of a pavilion among a regiment of infantry at Clermont-Ferrand. In Neu-Breisach in the years 1847, 1858, 1869 and 1870, an epidemic occurred in every fresh regiment that arrived, appearing as a rule in summer or autumn. Bottini observed an epidemic among the prisoners in Pallanga. In all cases these epidemics have occurred in barracks, prisons or seminaries, the inhabitants of the town not being affected. In nearly all cases these epidemics occurred in districts where goitre was endemic and among persons who had come from a nongoitrous district, who are liable to an

acute attack which soon disappears after leaving the goitrous district. It has also been observed that persons afflicted with goitre may partially or entirely lose their goitre on removing to a nongoitrous district. Horses, dogs, pigs, goats, cats and sheep have been observed to acquire goitre on being brought into an affected district, which gradually subsides after a week or a month.

Goitre is endemic in certain districts of nearly every country in the world, being more especially pronounced in the deep river cut valleys descending from high mountain ranges where the river water has become stagnated and formed marshes. In Europe the valleys of the Alps, the Pyrenees, the Carpathians, in the Black Forest, in Thüringen, in the Hartz mountains, in Sussex, Hampshire and Derbyshire in England it is particularly prevalent. The valleys of the Apennines are an exception, it being very rare in mid-Italy. In Russia it occurs in Finland and in the Eastern provinces. In Asia it is met with in the valleys of the Himalayas, in Tibet and in Siberia, in Japan, Sumatra, Ceylon and Java. In Africa, in Morocco, Abyssinia, in the Niger valley, in the Azores and in Madagascar. In North America it is found in Canada, in the Hudson Bay territory, in Connecticut, Michigan, New Hampshire, Vermont and Mexico. In South America in the valleys of the Cordilleras, in the central parts of Brazil and in Chili. Franklin observed it in Greenland, so that no zone is free from it. Altitude appears to have little effect, it having been observed in the Himalayas 4000 feet above sea level.

A disease which is so universal, and which incapacitates so many citizens, besides being accompanied by cretinism, a still more terrible affliction, has naturally been the subject of much scientific research. The etiology of the endemic goitre and cretinism has exercised the minds of pathologists ever since scientific observations were made

upon disease. Such an evident and unsightly deformity and the deplorable and pitiable condition of the cretins has caused an immense amount of experimentation and theorizing. St. Leger has collected no less than forty-two different views on the genesis of goitre. Light, air, season, temperature, race, configuration of the country, trauma, continued artificial pressure on the neck from the carrying of loads on the head, etc., have all had their advocates, but as yet no very satisfactory theory has been brought forward. In the Alps the natives ascribe the disease to the drinking of snow or glacier water but as goitre is endemic in countries where there is no perpetual snow and no glaciers this cannot be the primary cause. There is, however, much evidence to show that it is the result of drinking water which rises or passes over certain geological strata, viz: the marine sediments of the paleolithic trias and tertian formations. Others again claim it is due to a specific organism in the waters of the affected districts. Virchow is of opinion that the drinking water is the medium through which the disease is produced and that the geological conditions in which the water rises or through which it flows are the primary cause. Kocher is of the same opinion. Lücke claims the disease to be of micro-organic origin, and that the organism only grows on a specific medium, entering the body with the drinking water. The Sardinian commission on goitre and cretinism concluded that no geological formations were entirely free from the disease but that it was more prevalent on the tertian than on the more recent strata. Bircher, after the most careful and painstaking research, is of opinion that endemic goitre is confined to definite geological formations, viz: Devonian, Silurian, coal dyas, trias and tertian; that it does not appear on volcanic or crystalline rocks, on the river sediments or chalk formations nor on the quaternian or fresh water sediments.

Drinking water is considered by all observers to be the medium by which the disease enters the system, a very important proof of which is that certain wells in the affected districts produce the disease when their water is used for drinking purposes; so well is this recognized by the inhabitants that it is a common practice for men to drink from these *Kropfbrunnen* so as to acquire the deformity, thus escaping military service. These wells have been known from the earliest times, Vitruvius writes "*Acqueculis in Italia et Alpibus nationi medullorun est genus aquæ quam qui bibent effecuentur turgitis gutturi-bus.*" It has also been observed that families or individuals in affected districts who abstain from drinking from the *Kropfbrunnen*, using cistern water instead, remain free from the disease, and even those who have already acquired the disease are cured or relieved by abstaining from the affected water. In some districts goitre has entirely disappeared on the inhabitants obtaining a fresh water supply. An instructive example of this is the case of Ruppertsweyl near Aarau, which changed its water supply in 1884, drawing it from a goitre-free district. The reduction in the affected children was most marked. In 1885 59 per cent were goitrous, in 1886 44 per cent, in 1889 25 per cent, in 1895 11 per cent. Against the theory of the origin of the disease being in the drinking water is the fact that certain places drawing their water from the same source as a goitrous district are goitre free, which is possibly accounted for by the tributaries of the stream either diluting the water on its way to the unaffected district or by a tributary from an infected spring bringing the infection into the stream before its arrival at the affected area.

Many experiments have been made to produce goitre in animals. Bircher gave five young dogs water from a *Kropfbrunnen* for a month, as well as mixing the sediment



of the well with their food but none of them developed the disease, which he explains by the short duration of the experiment and by the animals being too young, goitre not usually developing in the child before the fifth year. Lustig and Carle experimented with a horse and found that by giving the water from an infected well one lobe steadily and progressively enlarged; this they removed when the other lobe began to enlarge, returning to its normal size on giving the animal ordinary water. Thirteen dogs were treated in the same manner, only one developing an enlargement of the left lobe, and on its removal the right lobe began to swell, but returned to normal on filtering the water. Ten other dogs remained normal on being fed with boiled or filtered infected water. These experiments are not conclusive, the number of animals developing goitre is very small and it has been observed that animals in goitrous districts that show enlargement of the gland usually become normal in a few weeks without change of environment.

From the above it seems most probable that the water which arises from or passes over certain geological formations contains a "something" which produces goitre. The nature of this "something" has been investigated with the following results:

Zschokke observed that the inhabitants on the right bank of the Aar were more subject to goitre and cretinism than those on the left; only this difference could be observed that the water on the right bank was more contaminated with animal and vegetable extractions than the left. Blondeau and Tinot analyzed the inorganic constituents of infected wells for lime salts, carbonates, phosphates, magnesia, etc., but obtained no constant results. Chatin in 1852 found that the water from the mountains and in the valleys affected contained less iodine than normal, which is of interest in connection with Baumann's dis-

covery in 1896 that the thyroid contained iodine. Later investigations show so many exceptions that the absence of iodine cannot be considered as a cause. These analyses show that the inorganic salts of the drinking water have no connection with the disease.

Humboldt considered that goitre and cretinism were the result of an infection. Vest, Bramberg, Schausberger, Troxler and Hirsch were of the same opinion. Virchow believed that the vapor contained a substance which acted upon the organism as a miasma. Lücke maintained that the miasma of goitre was similar to the marsh miasma of malaria.

The bacteriological examinations of the waters of infected springs have not yet produced any definite results. Klebs found an infusoria which he named *naviculicula*, Bircher a diatom *eucyonäma*, also a comma-shaped bacillus with snake-like movements, but all efforts to produce the disease in animals with cultures failed. Tavel examined clear water from springs which produced the disease and isolated thirty-three different bacteria, while in neighboring wells he could only find nine. Still none of these were apparently capable of producing the disease. Lustig and Carle examined twenty-five wells in the valley of Aosta by modern bacteriological methods. They were unable to find the bacillus of Bircher. They found, however, a bacillus which was constant, liquefying gelatin, but which produced no effects when injected into animals in pure culture.

The etiology of endemic goitre is still not proven, the weight of evidence points to the water which springs from or passes over certain geological formations being the means of entrance into the system of some contagium vivum which has as yet escaped detection.

Occasionally in districts where goitre is endemic it may be congenital. Demme records 37 cases out of 642 goi-

trous children that he examined. When congenital it may be so large as to interfere with delivery, growing with extreme rapidity, causing compression of the trachea, which may be fatal. It is usually hyperplastic, though Demme has observed both the cystic and mixed forms. Its weight at birth may reach 10 to 20 grms., the normal being from 2 to 5 grms. Virchow and Bednar found an enlarged thy-



FIG. 16.—Circular stricture of the trachea from goitre. (Demme.)

mus present in most cases; Eulenberg and Libert found persistence of the thymus in goitrous children and in adults. The persistence of the thymus has been observed in cases of Basedow's disease, and Ohlmacher finds it in cases of so-called idiopathic epilepsy with lymphatic constitution.

Sporadic goitre is a totally different disease from the endemic form, having no connection as far as is known with any specific infection. It is usually observed in young chlorotic girls who have developed early, and is probably the result of sexual disturbances, often suppression or partial suppression of the menses, trauma or hyperemia of the gland. The nature of the employment may have

some connection with the production of sporadic goitre. Hahn observed in Luzerches that goitre was a common affection among the workers in needle factories; since this form of industry has ceased in the district the deformity has disappeared. There is another form of

goitre which is occasionally observed in acute diseases which will be described later.

The enlargement of the gland may be unilateral, bilateral, or median, extending in various directions. In some cases no deformity may be visible and even its detection by palpation is attended with much difficulty. In the median form the swelling extends in the direction of the suprasternal notch, entering the mediasternal region. In these cases the gland moves with the respiration and may entirely disappear on deep inspiration. This form is termed by Fodéré "goitre endodans" or "goitre plongeant." In other cases the swelling may be held fast by the surrounding tissues under the sternoclavicular articulation and the first rib, causing great pressure on the gland, preventing diagnosis by palpation. Occasionally it descends into the pleural cavity as far as



FIG. 17.—Bayonet shaped trachea from bilateral goitre. (Demme.)

the aortic arch, pressing on the lung. It may extend into the submaxillary region, making but little visible deformity, though reaching as far as the mastoid process. This is the most common direction of enlargement in children and in congenital cases. Another form is known as movable goitre, "Wandernden Kropf" of Wölfler, the result of excessive mobility of the trachea and larynx, so that at one time it may be behind the sternum and at another in

its normal position, differing from the "goitre plongenat" in the regularity of the latter's movements with the respiration.

Goitres may grow to a great size, it being not uncommon to see one the size of a small child's head hanging as low as the breasts. When only one lobe is enlarged it is usually the right, the disease as a rule commencing



FIG. 18.—Showing the enlarged veins in goitre. (Wölfler.)

in this lobe, a possible reason being that the venous return from the right lobe is more interfered with owing to the relation of the vein to the heart. As the goitre increases in size so does the circumference of the neck, the sternohyoid, sternothyroid and sternocleidomastoid muscles being pressed forward and outward, usually atrophying, but in some instances they become hypertrophied, producing

great pressure upon the gland and through it on the trachea, being occasionally the cause of sudden death.

In nearly all cases of goitre the most pronounced symptom is the interference with the respiration, which may be caused in three ways, the prolongation of the trachea in relation to the larynx; narrowing of the lumen of the trachea; changes in the walls of the trachea; in severe cases all three may occur. Simple prolongation of the trachea in relation to the larynx is usually not accompanied with severe symptoms, but when accompanied by distortion of the trachea and consequent narrowing of the lumen the respiratory symptoms are much more severe. The contraction can be



FIG. 19.—Bending and narrowing of the trachea by goitre. (Demme.)

either unilateral, bilateral or circular, sometimes taking the form of the letter D, at others becoming half-moon shaped. In double seated compression the trachea assumes a bayonet shape. Compression of the anterior of the trachea is rare, being due to enlargement of the isthmus of the gland. After the compression has lasted some time trophic changes in the wall of the trachea take place so that the rings become soft, the trachea kinking as it were, sometimes causing sudden death.

At autopsy in these cases the microscopical examination shows hyperemia of the mucous membrane, fatty degeneration of the rings and also of the muscles of the posterior wall of the trachea. One of the results of the narrowing of the trachea is an enlargement of the lower portion of

the tube followed by chronic bronchitis. Very rarely the larynx is also compressed when the same degenerations

occur. Pressure on the esophagus and consequent narrowing with degeneration of the walls may occur, causing difficulty in swallowing; complete occlusion of the esophagus has been recorded.

The arteries and the veins of the gland suffer from dilatation, the walls becoming thin and brittle. The auricles dilate and dilatation or hypertrophy of the heart, with fatty degeneration of the heart muscle, occur in a large proportion of cases.

Of the nerves the recurrent laryngeal, the superior laryngeal, the vagus, the sympathetic and the hypoglossus are affected in certain cases.

The degenerations of the gland in goitre are of the nature of an hypertrophy with hyperplasia of the glandular constituents, the result of hyperemia. The changes

are various, resulting from the increase of the separate constituents of the gland, either of the parenchyma, the colloid substance or of the connective tissue, which may be classified into four forms, but which are rather a question of degree than of definite pathological lesions.

Struma parenchymatose seu follicularis arises from a hyperplasia of the follicles, commencing by the formation of zones or grooves in the interstitial tissue, containing small empty follicles, lined with cylindrical or cubical



FIG. 20.—Goitre of accessory thyroids. (Adjutolo.)

epithelium, which increase in size, forming perfect nodules containing colloid. The septa of these follicles be-

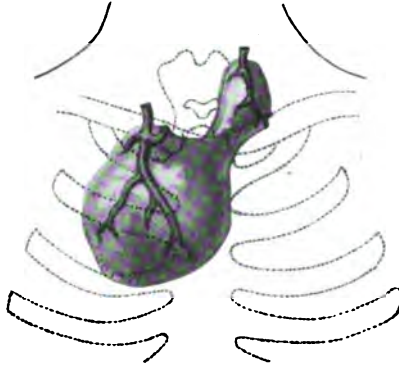


FIG. 21.—Retrosternal goitre in a deep-seated thyroid lobe. (Wuhrman.)

come thin; the epithelium disappears, the walls give way, forming larger follicles of irregular shape. Zielinska

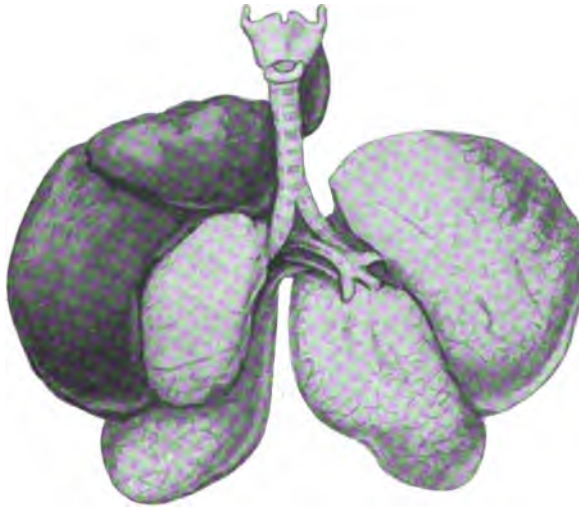


FIG. 22.—Intrathoracic goitre. (Dittrich.)

claims to have seen the colloid mass in the veins and arteries at this stage. The struma of the gland does not



differ from normal except in the formation of blood vessels and connective tissue, the latter surrounding the follicles and forming a nodule while the gland remains soft to the touch, rarely reaching any great size. There is only a graduated difference between this form and the

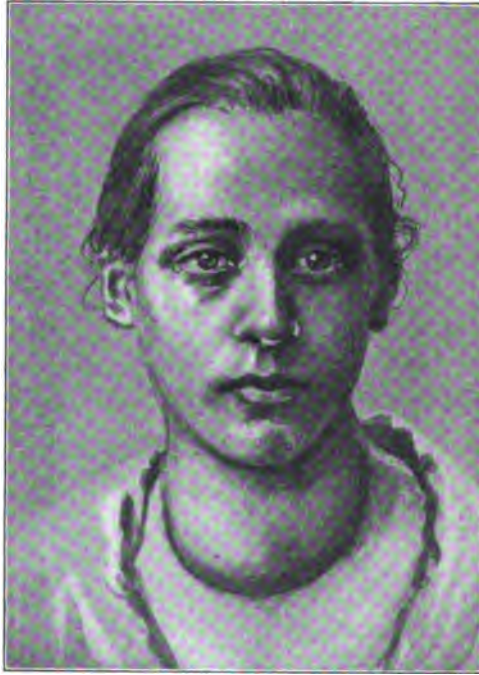


FIG. 23.—Follicular goitre. (v. Eiselsberg.)

struma gelatinosa seu colloides, the amount of colloid substance being greater, owing to a larger number of the follicles and alveoli coalescing from the atrophy and pressure from the excess of colloid forming struma cystica. Gutknecht differentiates another form of cyst formed by the breaking down of the walls of the alveoli by hyalin degeneration. The cysts consist of a capsule of fibrous connective tissue which, in the earlier stages, is lined with epithelium and filled with an opaque fluid containing fatty

detritus, degenerated red blood corpuscles, leucocytes, blood coloring matters, crystals of calcium oxalate, cholesterolin, ammoniomagnesium phosphate, sodium and potassium chlorid, of a brown or greenish color, showing that hemorrhage has taken place. In old cysts there is often calcification, which prevents the walls from falling to-

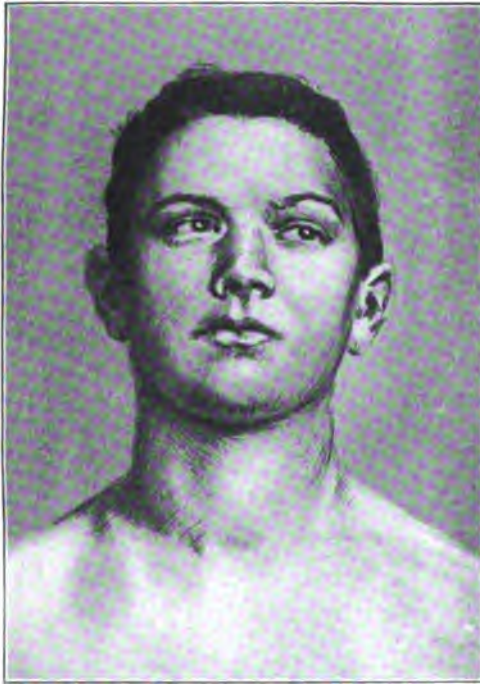


FIG. 24.—Goitre marked by diffuse follicular hypertrophy.

gether when the fluid is withdrawn, broken septa often remain in the cyst, showing on section an apparent network through the mass, which may also contain varicose veins, bleeding easily.

*Struma Vasculosa*.—In acute cases of hyperemic goitre the tumor fluctuates, pulsates, is compressible, and a murmur is audible on auscultation, while the neighboring vessels of the neck are congested. In chronic cases there is

an equal dilatation of both arteries and veins, the latter being varicose.

Struma fibrosa is produced by a hyperplasia of the interstitial tissue and is generally the result of or contemporaneous with a struma follicularis. In the centre of a nodule there is a yellowish cartilaginous shining spot of



FIG. 25.—Colloid goitre. (v. Bruns.)

connective tissue. Occasionally the connective tissue is diffuse. The nodules are scattered through the gland tissue in circumscribed areas, it being rare for the whole gland to be affected. Each nodule appears like an encysted tumor with a nucleus, in which are rings of connective tissue, from which strands pass toward the centre. The intermediate spaces usually contain follicles. The nodules are poorly supplied with vessels, but sometimes

are vascular and then contain extravasations of blood pigment, these ultimately becoming cysts. According to Gutknecht both the centre and periphery may break down and become calcified.

*Symptomatology.*—The symptoms of goitre are very varied in intensity, in many cases a very large goitre may



FIG. 26.—Follicular goitre with ectasia of the veins of the skin.

cause little or no inconvenience, except for the disfigurement of the neck, while a small retrópharyngeal nodule may produce the greatest irritation. In general, the goitre makes its appearance at or shortly after puberty, though occasionally as late even as the fortieth year, being more common in females than in males and may be either chronic or acute. The acute form is that described above

as hyperemia, appearing suddenly in a few hours or days. The tumor usually affects the whole gland, producing sometimes a loud circulatory murmur and by pressure dyspnea, generally disappearing in a few days, sometimes returning to become chronic.

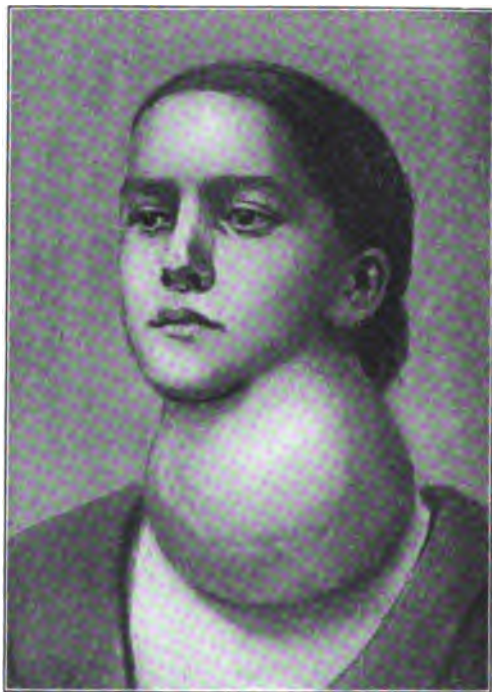


FIG. 27.—Cystic goitre. (Billroth.)

The chronic form makes its appearance slowly without attracting the attention of the patient either in one lobe or both, progressing slowly but surely to its maximum. At first no other symptoms are remarked except the deformity, with perhaps passing flushings of the head and face; as the gland increases in size the symptoms increase. In cases of small or medium sized goitres there is pressure on the veins of the neck in the neighborhood of the gland and on the lymphatics, producing dilatation of the veins,

cyanosis of the face, particularly on straining or after a heavy meal, headache and a feeling of anxiety. As the tumor increases in size symptoms of pressure on the trachea and paralysis of the glottis and vocal cords may appear, the latter caused by the pressure on the recurrent laryngeals. The pressure on the veins is sometimes very great and should one of them be opened it will spurt like



FIG. 28.—Cystic goitre. (v. Bruns.)

an artery. Should a tracheotomy become necessary the venous congestion ceases as soon as the breathing is restored. From the pressure of the tumor the position of the veins and arteries may be altered, the jugular being pressed toward the middle line of the neck and the carotid outward to a distance of 10 to 12 cm. where it may be possible to feel it. Irregularity, increased frequency and palpitation of the heart are common symptoms in young chlorotic girls, probably due to irritation or paralysis of

the vagus. Of still greater importance are respiratory disturbances which may come from direct pressure on the trachea, from nerve irritation or paralysis. The difficulty of breathing increases with the growth of the tumor and may be greater at one time than another. When a tracheal catarrh supervenes or the goitre is suddenly increased by hyperemia, which may occur from the exercise of running upstairs or walking uphill, very serious results are produced, requiring tracheotomy, or even death may supervene before the operation can be performed. There is also a stridor on expiration, which can be heard from a distance; as the pressure on the trachea increases so does the stridor. In advanced cases there is also a sound on inspiration; patients at this stage are compelled to inspire while talking quietly or to use expiration to say a word quickly, when there follows a long, rough whistling inspiration. If a laryngeal or lung catarrh supervene a serious condition may arise of dyspnea or asphyxia. The "goitre plongeant," or substernal tumor plays an important part, in some cases the tumor pressing the trachea between the sternum and the vertebral column. This only happens, however, when the tumor becomes fixed under the sternum. Pressure on the laryngeal nerves produces either an inflammatory thickening of the perineurium or an irritable condition of the nerve, still more often a pressure atrophy with resulting paralysis or paresis of the vocal cords. According to Wölfler this condition occurs in 10 per cent of the cases. This form has been called goitre asthma, producing severe symptoms of suffocation, through the reduction of the rima glottidis, combined with narrowing of the trachea. Examination with the laryngoscope shows paralysis of the muscles; in making a diagnosis, neurosis, hysteria, catarrhal conditions of the air passages, emphysema and congestion of the venous circulation must be excluded.

In the submaxillary form the posterior auricular nerve may be affected, causing pain behind the ear and in the occipital portion of the occipito-frontalis muscle. The sympathetic is also subject to pressure, producing hemi-crania and other disturbances; probably the exophthalmos of Graves' disease is in part at least produced by irritation of the sympathetic; occasionally the spinal accessory is affected, producing clonic spasms of the neck. Pressure on the esophagus from a retropharyngeal goitre may produce dysphasia to such an extent as to prevent the patient from swallowing, or a piece of food may be arrested in the lumen and have to be forced down with the sound. Wölfler found the narrowing of the esophagus in 13 per cent of his cases. There is a change of the physiognomy, which is of some diagnostic value, the head is thrown back, the neck stretched, the mouth widened and drawn backward, giving the face a stupid expression. There is also an intellectual weakness with mental irritability; epileptic spasms occur, whether connected with the disease or merely a coincidence it is difficult to say.

Considering the number and importance of the various tissues in the neighborhood of the gland, whose functions may be interfered with by pressure from the tumor, the number of symptoms which may be produced must necessarily be very great. As the enlargement may take place in such a direction as to become substernal, subclavicular, submaxillary or retropharyngeal palpation may be difficult or impossible. Pressure may be exerted upon the veins and lymphatics of the neck as well as upon the carotid arteries, on the pneumogastric nerve affecting the heart and the digestive function; upon the recurrent laryngeals, the superior laryngeals and the phrenic affecting the respiration; upon the glossopharyngeal, the posterior auricular, the spinal accessory, the sympathetic and very rarely the brachial plexus. It may produce con-



traction or occlusion of the trachea and esophagus, while an excessive secretion of the colloid material will produce the symptoms of thyroidismus, or, as is more often the case, the gland becomes cirrhotic, when the myxedematous symptoms of hypothyroidea and athyroidea will occur.

The diagnosis of goitre presents no difficulties, provided the enlargement is in such a direction as to be visible or palpable. The disease has to be differentiated from lymphomata of the neck glands, lymphosarcoma and the enlarged glands of Hodgkin's disease. The swollen glands can be differentiated by the position and shape; the slow growth, the cachexia and the condition of the blood help the diagnosis. Should the tumor be retropharyngeal the diagnosis may be impossible. In the absence of the isthmus the tumor no longer follows the movements of the throat. Wölfler gives the following symptoms in these cases: Suffocation, especially at night, pressure on the jugular by sinking the head, a feeling of pressure in the aperture of the thorax, a paralysis of the left recurrent laryngeal nerve, one side exophthalmos, fixed larynx, narrowed trachea, and in some cases the pulse of the carotid may be different from the radial.

For the differentiation of the different forms of goitre the following points are of service:

*Simple Hyperemia.*—Is transient, usually connected with menstruation or sexual causes; the throat becomes round and enlarged, the larynx is no longer prominent, the examiner feels only indistinctly the contour of the gland, which is either soft to the touch or unaltered in consistency.

*Struma Parenchymatose.*—Is of soft consistency with sharply defined borders, the size usually about that of a pigeon's egg, or it may increase to that of a hen's egg, in the latter case it is visible; this form is usually unilateral.

*Struma Vasculosa*.—Does not reach any great size, is compressible by the finger, feeling like a sponge, a circulation murmur can be heard on auscultation.

*Struma Colloides*.—Produces equal enlargement on both sides, the skin over the gland is tight, the jugular is dilated, the symptoms are those of hyperthyroidea.

*Struma Fibrosa*.—Contains hard nodules from the size of a pea to that of a hen's egg, with the conglomeration of the nodules the gland may grow to a great size, the separate nodules being distinct to the touch; in calcification the hardness is increased, the symptoms are those of myxedema.

*Mixed Goitre*.—Is the largest and is usually of the hanging type, extending sometimes as low as the breasts.

For the palpation of goitre it is best for an assistant to grip the back of the neck from behind, so that the gland does not slip from under the fingers of the examiner. Aspiration is occasionally used to determine the nature of the goitre, but it is not without danger.

The course of uncomplicated goitre is slow, it may be from early youth to old age, though the patient usually seeks surgical aid either before twenty or between twenty and thirty.

Besides the goitre of the true thyroid gland the accessory thyroids may become enlarged either separately or with the mother gland.

Accessory thyroids are of three kinds: those which are not connected with the mother gland, isolated or true accessory glands; those which are connected to the main gland by a band of connective tissue, false accessory glands, and those which are connected by a band of thyroid tissue, connected accessory glands. They can be further divided according to their positions in relation to the main gland—anterior, posterior, superior, inferior and lateral—or according to the anlage from which they were developed.

Accessory thyroids, derived from the middle or lateral anlages, can be either substernal, endothoracic or retro-clavicular, and are the most common. Occasionally the isthmus is lower than normal and when goitrous it lies under the manubrium sterni. As a rule the accessory gland grows downward from the isthmus analogous to the pyramid which grows upward. This form, when not connected with the isthmus, is sometimes called aortic struma; others are connected with the inferior apex usually of the left lobe and are in the thoracic cavity; endothoracic glands, reaching to the pericardium and usually lying behind the trachea; others may pass behind the trachea, pressing upon the lungs, and are termed intrathoracic, while others may be grouped behind the sternum. The posterior accessory glands may lie behind the larynx and esophagus, when a goitre will contract the esophagus; occasionally they occur within the larynx and trachea, and even in the substance of the hyoid bone. The diagnosis of goitre of the accessory glands is attended with great difficulty.

The thyroid gland is often in an abnormal position and may be so low as to lie completely behind the sternum.

The treatment of goitre is either prophylactic or medicinal, including organotherapy and surgical.

The prophylactic treatment consists in leaving a district in which goitre is endemic, in abstaining from drinking the water or boiling it thoroughly first. If there is a disposition to goitre, the patient should abstain from any exercise which may produce hyperemia of the neck. Removal to the seacoast is often curative in the early stages.

Of drugs iodin has been used for many years, at first empirically, being given as powdered sponge, which contains iodin in organic combination (spongin). Coindet, of Geneva, in 1820, was the first to recognize that the iodine was the active principle, and since his time the iodides

have been the orthodox treatment. Kocher, who has made a special study of the disease, and has had an exceptionally large experience, is of opinion that 90 per cent of all goitres can be cured or improved by iodine treatment, so that only 10 per cent need come to the operating table.

Iodine can be administered either by external application, by the mouth or by injection.

A satisfactory method of applying iodine externally, preventing the disfigurement by staining the skin, is to apply a bandage soaked in from 10 to 20 per cent solution of potassium iodine during the night.

Monal, Mill and Gove have used a salve containing about 3 per cent biniodide of mercury with good results, even in congenital cases. Gussenbauer recommends iodoform ointment. The internal administration of iodine is more effective either in the form of potassium or sodium iodide, Lugol's solution or iodoform, but only in small doses, care being taken not to produce iodism. The treatment only gives satisfactory results in young people and at the commencement of the disease. The colloid and fibrous goitres are not influenced by iodine treatment.

In 1873 the English physician, Mosen Indenland, gave the fresh thyroid gland of the sheep in some cases of goitre with good results. Emminghaus and Reinhold, having observed the improvement in the mental condition in cases of cretinism and myxedema by the administration of thyroid, administered it to some goitrous insane patients. The mental condition of these patients was not improved but the goitres disappeared. v. Bruns administered thyroid tablets to 350 goitrous patients and found 8 per cent cured, marked improvement in 36 per cent, slight improvement in 30 per cent, no improvement in 26 per cent. The treatment produced the best results in young patients with follicular hypertrophy. In struma fibrosa the nodes were not reduced in size, but the intermediate tissue was

absorbed, reducing the size of the goitre, rendering operation unnecessary.

v. Bruns studied the action of the thyroid treatment on twelve goitrous dogs by removing a portion of the gland before and after treatment and found that the effect of the feeding was to increase the amount of colloid in the tissue of the struma, it being apparently greater than in the normal gland, the lymphatics being gorged with colloid, the undeveloped tissue was absorbed, the vessels partially obliterated. The total result he described as a trophoneurotic atrophy of the gland. Kocher excised a colloid goitre after several weeks' treatment with thyroid and found that only a portion of the alveoli contained colloid, and those that did contain colloid were only from a third to a quarter full. He came to the conclusion that there was no difference between the action of the thyroid and iodine. Kijewski saw symptoms of Basedow's disease during treatment. K. Serapin found that colloid, cystic and vascular goitre were not benefited, but that the fibrous goitres became somewhat softer and smaller.

v. Mikulicz claims to have good results from the administration of thymus.

The direct injection of tincture of iodine or iodoformol into the gland was first introduced by Sköldberg in 1855, and later by Luton in Rheims and Lücke in Strassburg.

Pring investigated the effect of the injection of iodine into the glands of animals. He found that two or three days after the injection of 0.2 ccm. of tincture of iodine there was a serofibrous exudation at the point of puncture with necrosis of the cells of the parenchyma, which necrosis did not take place if salt solution were used instead of the iodine. After one or two weeks there was a formation of connective tissue. After the injection of alcohol there were the same results, but to a less degree. After the injection of iodoform there was parenchymatous

coagulation necrosis without fatty degeneration of the cells. The colloid substance was not absorbed as a result of the injection. The injection is not without danger, as sudden death may occur if the injection is made into one of the larger vessels. Another danger is that the injection may go into the trachea. The operation must be performed under strict antiseptic precautions. The danger of injection into a vessel can be guarded against by withdrawing the canula and observing if it is followed by blood; if so, another place must be chosen for injection. To be sure that the needle is in the goitre it is necessary to notice if it moves when the patient swallows.

The injections are usually given twice a week, the first injection should not contain more than 0.25 to 0.5 grms. tincture of iodine, gradually increasing to 1.0 gm. of the tincture or 3.0 grms. iodoform solution.

The action of this treatment is usually very slow, it being often three or four weeks before any improvement can be noticed. The results are satisfactory in a large percentage of cases in struma follicularis, but is of no value in struma fibrosa. Gairé treated 140 cases, in 90 per cent all symptoms of trachea stenosis disappeared. He used a solution of iodine 1.0 gm.; ether, 7.0 ccm.; olive oil, 7.0, which must be kept in dark-colored bottles and carefully stoppered. Alcohol injections have been recommended by Schwalbe. Ergotin, strychnin, osmic acid, Fowler's solution, 1 per cent carbolic spirits, carbolic acid, papain, permanganate of potash, ferric chlorid, chromic acid have been tried but with unsatisfactory results.

## CHAPTER VI.

### SURGERY OF THE THYROID GLAND.

When medical treatment has failed surgical interference may become necessary under special circumstances. If the dyspnea is so constant as to incapacitate the patient for following active employment, or one of a sedentary kind especially, such as involves the bending of the neck so that the patient is prevented from earning a living, and if the disease is progressive an operation should be advised. Should there be tracheal stridor accompanied by a goitrous isthmus or extension of the swelling laterally or downward, there are often sudden attacks of dyspnea, which may end fatally before assistance can be given. These sudden attacks of dyspnea are due to some extra exertion which calls into action the additional muscles of respiration, the sternocleidomastoid, the sternohyoid and the sternothyroid, which, pressing on the goitre, produce still further narrowing of the trachea, thereby increasing the dyspnea, and as the dyspnea increases the action of the muscles becomes still further increased, producing closure of the trachea and death. Another cause of sudden enlargement, increasing the dyspnea, may be sudden extravasations of blood into the goitre.

In emergency it is best to slit the deep cervical fascia and to raise the muscles that press upon the gland, allowing it to bulge forward away from the trachea; at the same time should there be cyanosis venesection should be resorted to. If the foregoing do not give relief either the gland or isthmus or both must be partially removed, or tracheotomy performed, if the patient's condition will admit of the operation. Tracheotomy is often very difficult

under these conditions. Should the enlarged isthmus permit of the operation above the gland there is usually no convenient canula at hand, a large rubber catheter may be used or a Durham's canula with a rubber attachment; should there be substernal enlargement König's catheter should be substituted as soon as possible. Opening the trachea below the isthmus is often impossible when the gland is much swollen, reaching as it often does from the cricoid cartilage to the manubrium. To divide the isthmus and then perform tracheotomy is attended with great danger of hemorrhage followed by septic pneumonia. The dangers of low tracheotomy consist in the number of large vessels, such as the innominate artery, which may be accidentally cut, as well as of injury in the confined area to the dilated vessels of the gland itself, while the danger of pneumonia is increased. Should the goitre be unilateral it is probably due to adenoma or cyst; in the latter case it may be drained or removed, in the former the tumor should be enucleated if possible, if not the lobe must be removed. Removal of the isthmus may not relieve the symptoms. Should this be the case one lateral lobe should be entirely removed. It is probably better should the condition of the patient permit to remove the isthmus and one lateral lobe at once rather than resort to tracheotomy, as the latter invariably causes a septic wound and very often produces pneumonia.

Another indication for operation is the steady enlargement of the gland, with or without dyspnea, especially if the enlargement is in the downward direction where it will become substernal. The lower the growth extends the greater is the danger of mediastinal cellulitis after operation and the less chance of giving relief by tracheotomy in emergency cases. Another symptom which indicates operative treatment is the inability to stoop without a sensation of blood to the head; the inability to sleep



lying down so often associated with asthma, is also a serious symptom. In the first instance the feeling of rush of blood to the head must be due to pressure on the gland, which in its turn presses on the jugulars, and in the second the weight of the gland pressing upon the laryngeal nerves may be the cause of the asthma and discomfort. When the tumor is very large there is often a dragging pain at the neck, sometimes without any other symptom. The questions which the surgeon has to consider are the probabilities of a sudden and perhaps fatal attack of dyspnea, and if the tumor is progressive, in both cases he is justified in advising operation after fully weighing the dangers of the operation, which are increased under the following conditions:

If the goitre is very large, and especially if it is fixed on a broad base, if the goitre is calcified, or if its limits are indistinctly defined, the risks of operation are materially increased. In those cases which are substernal the risk of mediasternal cellulitis is great. The age of the patient is also of moment, Billroth being of opinion that no operation should be performed after the age of forty unless there is malignant disease, and as malignant disease only attacks unhealthy glands he would operate early. On no account should the operation be performed for the sake of the personal appearance only above this age, but in early adolescence when the gland is not very large, it is permissible for fear of future dyspneic symptoms or malignant growth. Patients with feeble pulse, which is the result of pressure on the veins and trachea and from the intervention of a more or less voluminous vascular network producing strain on the heart, are apt to succumb to the operation.

There are a number of cases which appear to be allied to Basedow's disease but which have not the typical symptoms and are to be operated upon with caution, there being

greater risk of excessive action of the heart, pyrexia, and perhaps lung trouble. These cases are usually young patients with a soft parenchymatous goitre affecting the whole gland, with marked vascularity, pulsation, a pulse of 90 or more, the heart easily excited, with a soft systolic bruit. These are cases which are suffering from hyperthyroidea, and are distinct from other forms of goitre. After the operation the patient is restless and depressed, there is a constant effort to clear the throat by coughing, which disturbs the wound; he feels a dread of suffocation from the accumulation of mucus in the trachea and larger bronchial tubes; the pulse runs up to 120 or 130, the temperature rises, which is followed by exhaustion and death. Should the patient survive the wound does not heal by primary union, there is a profuse blood-stained discharge for several days, though it may not be infected. These symptoms are not uncommon after operation for Basedow's disease and are probably the result of a quantity of colloid substance having been expressed out of the gland during the operative manipulations. Great care must be exercised in handling the gland so as to prevent pressure causing the exudation of the colloid substance, and the wound washed out with sterilized water. It is well to place some absorbent cotton in the wound, renewing it every two or three hours so as to prevent any further exudation from entering the system. If this is attended to the symptoms, which are those of thyroidismus, will disappear.

In case of partial extirpation or enucleation the wound usually heals well and the respiratory symptoms are relieved, the constricted trachea returning to normal in a short time. Should there have been paresis of the laryngeal nerves from pressure of the goitre and consequent failure of the voice there will usually be a return to normal. Krönlein found that out of 25 cases of inhibition of the vocal cords 21 returned to normal after the operation.

The operation for the removal of goitre was for a long time considered, and not without reason, as being one of the most dangerous attempted, but, thanks to antisepsis and asepsis, special technique and the recognition of the cause of tetany and cachexia strumipriva, which at first so often followed the operation, the mortality in the hands of good operators has fallen to almost nil. Billroth, of Vienna, and Kocher, of Berne, have been the two surgeons to whom is due this most satisfactory result. Kocher had no mortality in 272 consecutive cases, Krönlein in 200, Roux in 526 operations had a mortality of 1.27 per cent; v. Mikulicz in 151 2.6 per cent; v. Bruns a mortality of 2.0 per cent. Riverdin collected the statistics and found that in 6103 operations the mortality was 2.88 per cent. Riverdin also gives the statistics of 93 cases of death from the operation, 42 being from suffocation, asphyxia or pneumonia, 19 from hemorrhage, 13 from wound infection, 9 from shock and wounding of the recurrent laryngeals, 6 from heart syncope and 4 from tetany or myxedema.

The most dangerous complication during operation is hemorrhage, which can be guarded against by a sufficiently large incision, adequate retraction or division of the overlying muscles, and by identifying the capsule. The latter is often difficult, the layers of the deep cervical fascia over the tumor vary in thickness and number, each one must be divided carefully till the tumor is reached, which can be recognized by its purple red color, its consistency and the way the vessels stand out and ramify over the surface. The arteries are usually easy to manage but the veins give great trouble, being very numerous, thin-walled and are met at every step of the operation. When the growth is soft as well as vascular any opening of the capsule is apt to flood the wound with blood, making it difficult to find the bleeding point, increasing the danger of including the nerves within the ligature. Asphyxia and aphonia may

occur from including a recurrent laryngeal nerve within a ligature, cutting the nerve or bruising it. Aphonia may be the result of wounding the inferior laryngeal or dragging on it; possibly section of the cricothyroid branch of the superior laryngeal nerve may also produce aphonia. Months after the operation these symptoms may appear, owing to inclusion of the inferior laryngeal nerves in the cicatrix. There is also a progressive ascending neuritis of these nerves which may have commenced anterior to the operation, due to compression of the goitre. When the growth is large or when fixed by adhesions or attached by a broad base the nerves are apt to be injured; also when the tumor is ill-defined or encircles the trachea and esophagus closely, as it usually does when the disease is malignant.

Even after every care postoperative hemorrhage is not uncommon so that it is requisite that the patient be carefully watched, any change of color or weakness of pulse calling for immediate examination. The venous hemorrhage is possibly even more dangerous than the arterial, owing to the possible formation of air emboli, which may cause sudden death, the veins in the neighborhood of the operation being without valves and the vessels dilated. Treves recommends washing with normal salt solution and leaving it in the wound, so that it will be aspirated into the jugular instead of air. Should the recurrent laryngeal nerves be accidentally cut during the operation paralysis of the vocal cords will follow. Wounding of the superior laryngeal nerves and of the sympathetic has to be guarded against. In the first case anesthesia of the lining membrane of the larynx will ensue. Wounding of the sympathetic produces postoperative ptosis, one-sided widening of the pupil and sinking of the eyeball. In a case in Billroth's clinic there was narrowing of the pupil, a difference of temperature between the right and left side of the

face, congestion and heat on the operated side, combined with heavy sweating and increased secretion of the saliva. Should the hypoglossal nerve be injured paralysis and atrophy of one half of the tongue will occur.

The most dangerous of the postoperative complications is infection of the wound, which may result from faulty technique; from the vomiting of the patient into the wound, or from wounding of the esophagus. Should it have been necessary to perform tracheotomy the probabilities of infection are very great. In many cases death follows rapidly on infection, which may extend into the mediastinum, causing dyspnea, severe pain under the manubrium sterni, pain on pressure, sweating and high fever. The wound must be at once thoroughly opened and cleaned. Hyperthermia to about 38 degrees C. is common in thyroid operations. Bergeat observed it on all but three out of 249 operations, other surgeons observed it in from 60 to 80 per cent of their cases. It seems probable that this hyperthermia is the result of the gland being squeezed during the operation, causing exudation of colloid and is really the result of hyperthyroidea. Sometimes there is very difficult breathing after the operation, which may be due to too tight bandaging, too much tampon in the wound, to postoperative hemorrhage, which, by producing a large hematoma, may press on the trachea or, in cases of tracheotomy, bleeding into the trachea. In other cases there is an accumulation of mucus, which requires that the pharynx be washed out with the head hanging downward; this complication predisposes to pneumonia. Occasionally the trachea may kink through some sudden movement of the head.

A complication which is to be dreaded is pneumonia, which may develop very quickly, when it is probably caused by venous sepsis. As a rule, however, it develops slowly during the first few days after operation; paralysis

of the larynx through injury of the recurrent laryngeal nerves is a predisposing cause, as during sleep the glottis is open, the saliva and mucus from the mouth flows into the trachea. Wölfler injected human saliva into the trachea of rabbits, but failed to produce pneumonia; on the other hand, if infected substances were injected lobular pneumonia followed. Difficulty and pain on swallowing is usual for the first few days after operation, when it gradually disappears.

The administration of an anesthetic is a point which requires much discretion and is still debatable. The danger of excitement at the commencement of anesthesia increasing the respiratory disturbance causing risk of asphyxia has to be borne in mind; often the condition of the lungs from chronic catarrh or emphysema, as well as dilatation of the right heart, cause the surgeon the greatest anxiety. The venous stasis, already severe, will be increased, while vomiting may cause sudden death. Many operators use no anesthetic, on the ground that the handling of the goitre is almost painless, the pain being only at the first incision and the luxation of the tumor; others use cocain, Schleich infiltration or other methods of local anesthesia. In some few emergency cases patients are brought to the table in a semiasphyxiated condition, when the danger of anesthesia is so great that the surgeon will be compelled to operate either with local anesthesia or with none, but these are few and far between. In any case the patient must be placed in the position in which the difficulty of breathing is least, which the patient is usually able to explain, and may be either sitting or extended; the head should be firmly fixed so as to prevent any sudden motion. A bolster is placed under the neck and the hands held by an assistant. Every care must be taken not to excite the patient. There should be a protector placed between the face and the field of operation to prevent infec-

tion from the saliva or from the patient vomiting into the wound.

The parts having been prepared, the head and shoulders conveniently supported and secured against movement, a free incision is made along the anterior border of the sternocleidomastoid over the most prominent portion of the tumor, avoiding large veins. An ample longitudinal incision will usually be sufficient and leave little noticeable disfigurement, as the scar will fall into the sulcus internal to the muscle. It is rarely necessary to make more than the longitudinal incision. The skin and platysma are cut, the superficial veins tied, the deep fascia divided, and the hyoid depressors separated or divided. If necessary the patient will usually begin to breathe more easily. It is of importance that the opening, both in the skin and in the fascia, should be ample, giving plenty of room to prevent the squeezing of the gland, which may cause the serious consequences mentioned above. The goitre on being laid bare can be recognized by its blue red color and large veins, which stand out as they ramify over the surface of the gland.

The sternomastoid is retracted, drawing out the large vessels, then with his finger or blunt scissors the surgeon frees the tumor from its bed, shelling it forward, probably finding that it is only fixed above, below and internally. Care must be taken to work gently and to keep close to the tumor. As the veins are distended and the walls thin great care must be exercised not to injure them, and on no account must the capsule be broken. Should this occur the wound is at once flooded with blood. The upper extremity is freed first, the superior vessels ligated, either doubly with chromic gut passed with an aneurysm needle or divided between two pairs of forceps, both ends being tied. The tumor must be isolated in a downward direction and any portions which may exist under the sterno-

mastoid muscle turned out. It is better to now divide the isthmus, which can be done either by double ligature after transfixing with an aneurysm needle carrying strong gut or it may be torn through and each bleeding point tied. If it should be very vascular and large it should be subdivided and tied in several places, the ligatures interlocking; it may be seared through with the cautery or by an *écraseur*, the stump should then be treated with zinc chlorid or formalin, packed with sterilized gauze and brought outside the wound. The tumor is now drawn to one side and the inferior vessels dissected out; as the recurrent laryngeal nerve runs along with the inferior thyroid artery when near the gland the artery should be ligatured as near the axis as possible always examining carefully to be sure that the nerve is not included in the ligature. After the gland is removed all bleeding points must be stopped and the wound thoroughly dried out.

The wound even after removal of one lobe only is often very large and deep, the larynx, trachea, esophagus and large vessels all being exposed, as well as the dome of the pleura, and is difficult to drain properly, as it dips below the clavicle. In parachymatous cases, where the operation has been easy and the parts little disturbed, the surgeon will dispense with draining and trust to a dry wound and carefully applied pressure. The edges should be exactly brought into position to promote easy healing. The scar may become keloid, but this is only temporary, a white scar being the only disfigurement. The dressing in immediate contact with the wound should press evenly, distributing the discharge over a large surface of dressings and obliterating the cavity. In order to keep the dressings in position the bandage should be passed under the axillæ, using a pad, and then wound round the chin and forehead and made secure with stitching; this prevents the bandage slipping and exposing the upper half of the



wound. Under the chin should be a protector to prevent the dressings being soiled by the saliva, etc. Should, however, the parts be much disturbed during the operation drainage is advisable. In cases where there may be exudation of thyroid secretion the sutures may be left long and untied, the wound plugged with sterilized gauze, and after a few days the gauze may be removed and the sutures tightened.

Tracheotomy should never be performed except in most urgent cases, as the results are almost always fatal from septic infection of the wound, septic bronchopneumonia and partly from increased shock. If apparently needed the surgeon should first divide the fascia and muscles and endeavor to ease the pressure by letting the tumor bulge forward. The tracheotomy wound requires great care and attention; the wound must be left open and washed with bichlorid 1 to 4000 very frequently, but in spite of all precautions septic infection will ensue.

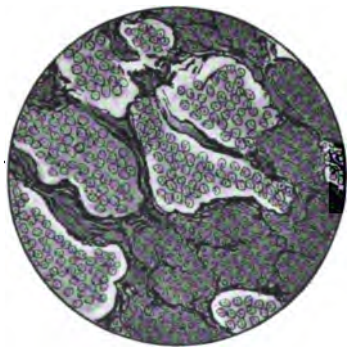


FIG. 29.—Struma Vasculosa.

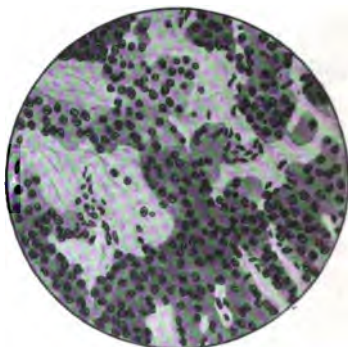


FIG. 30.—Adenoma of Thyroid.

Enucleation of thyroid adenomata has been advocated by Porta, Billroth, Socin, Riverdin, Wölfler, on the ground that there is less danger of wounding the nerves and hemorrhage, and also that there is certain to be enough active thyroid tissue left to prevent tetany or cachexia strumi-

priva. As early as 1804 Brüninghausen enucleated a cyst; in 1884 Billroth had performed 8 operations successfully.

In ordinary cases of solid enlargement of the thyroid encapsulated adenomata are often present, which can be comparatively easily enucleated, and is a much less severe operation than the partial removal of the gland. The incision is the same as in the partial removal, the fascia being divided in the same way. On the gland being exposed it is necessary to examine and palpate carefully in order to define accurately the limitations of the capsule of the adenoma. Usually it is easily recognized, rarely the side of the gland will have to be raised and explored. The adenomata can be recognized by its smooth white covering. Adenomata may be multiple, in which case each must be enucleated separately, or those left behind will continue to grow and necessitate a second operation. After enucleation the gland does not shrink so completely or permanently as after the extirpation of one lobe and half the isthmus. The operation of enucleation is not applicable to the gelatinous form and should never be tried unless the adenoma can be distinctly defined. It is rare that cysts or adenomata occur in bilateral goitres, they being usually unilateral. Patients suffering from unilateral goitres rarely seek operation, as the dyspnea is not severe. On the whole partial removal of the gland is preferable, giving better results and less probability of a return.

Removal of the isthmus alone is often followed by shrinkage of the tumor and has the advantage of requiring less preparation, enabling the surgeon to give relief in emergency cases, when the slitting of the skin, muscles and fascia has failed to give relief without much assistance. It is preferable in cases of very large growth, when anesthesia is dangerous and time is short, or when

the enlargement of the isthmus is the cause of the tracheal stridor.

In cases of malignant disease the dangers of the operation are much increased, as the growth hugs the trachea, dipping into the sulci between the large vessels and the trachea, infiltrating important parts, often growing into the mediastinum. Under these conditions the probabilities of wounding the nerves and vessels are very much increased.

Another form of operation, which has recently been advocated and practiced with success, is ligature of the arteries of the gland, leaving the tumor in situ. This operation has given contradictory results, splendid results being opposed by utter failures. The failures are due to the existence of abnormal arteries, as if all arteries are tied the circulation must cease, and the gland atrophy, but if the circulation is not cut off or reestablishes itself the operation will fail. Experience has shown that ligature of all the arteries does not produce gangrene.

The difficulties of the operation consist in the finding of the arteries, they varying much in position, in that the vessels are often diseased and in that the nerves are apt to be ligated with the vessels. The landmarks for the arteries are as follows:

The superior thyroid, the first branch of the external carotid, arises just above the bifurcation of the common carotid about one-quarter of an inch below the great cornu of the hyoid bone, covered at first only by thin fascia and the platysma, it ascends slightly and then curves downward, taking a tortuous course covered by the depressors of the hyoid bone and the sternothyroid.

The head should be raised and turned to the opposite side; the incision is made along the inner border of the sternomastoid muscle, with its centre corresponding to the upper border of the thyroid cartilage, the sternomas-

toid and large vessels are drawn outward and the omohyoid downward and inward, and the artery sought for in the hollow between the larynx and the carotid. Usually there are also present some enlarged veins of superior thyroid which will also require ligatures.

The inferior thyroid is more difficult to find. It is the largest branch from the thyroid axis of the subclavian, ascending tortuously inward behind the carotid sheath, the middle cervical ganglion lying in front of it. Before entering the gland it runs a short distance in close relation with its posterior surface, and the recurrent laryngeal is then in contact with it, often passing between the terminal branches of the artery; further, the left artery is often in close contact with the esophagus, while the thoracic duct, at first posterior, arches over the artery on this side to enter the subclavian vein. The tubercle of Chassaignac or the transverse process of the sixth cervical vertebra and the body of the fifth vertebra are landmarks for the point at which the artery enters the gland.

The incision is made along the anterior border of the sternocleidomastoid to the clavicle, as if to ligate the carotid low down, the fascia divided, the sternomastoid and the carotid sheath and contents drawn out. The head is then flexed to relax the carotid, the tubercle felt for and the artery sought for below, working with a director, the vessel exposed and then ligated. Great care has to be exercised as the artery is often degenerated and friable from pressure, and in order to avoid the nerve it is as well to ligate as close to the carotid as possible. The presence of the phrenic nerve has also to be borne in mind.

This operation seems especially useful in Basedow's disease.

Cysts of the gland, though usually only unilateral, may grow to a great size and require removal. Occasionally the injection of ferric chlorid gives good results, but there

is a risk of suppuration and cellulitis. Should the cyst not be of any very great size it may be excised, it turns out easily if it has not been previously blistered, when adhesions usually exist.

If convenient it may be emptied first and then, by squeezing the edges, turned out empty. After such an operation the lobe appears to be useless, but should on no account be removed but bandaged in such a way as to apply even but not excessive pressure. Should the cysts be multiple the whole lobe must be removed.

If excision is impossible incision must be practiced.

Clean up the operating field and cut down as previously described, carefully securing all bleeding points, slit open the cyst and examine. The contents may be either gelatinous or grumous, serous, mucoid or coagulable blood clot. On examination the wall of the cyst, if of long standing, may be so fibrous and evascular that sloughing may take place; on the other hand, it may be vascular. Should any of the vessels be wounded very suddenly, leaving no time for suturing, it will be necessary to plug at once. These cysts are difficult to heal from the bottom, the edge of the slit may be sewed to the skin, the inside curetted and packed lightly.

In all these operations there is very considerable risk from hemorrhage, from infection, from exudation of the colloid substance from the gland, from injury to the nerves and vessels, as well as the danger of asphyxia during anesthesia. As shown above the mortality from the operations is not large. Riverdin collected the mortality of the various operations, which are:

|  | Percent<br>Mortality. |
|--|-----------------------|
| Intraglandular enucleation .....         | 0.78                  |
| Combined enuclear resection .....        | 2.99                  |
| Partial extirpation .....                | 3.46                  |
| Resection according to v. Mikulicz ..... | 6.66                  |

There are two diseases which occasionally follow the complete excision of the thyroid gland, or if a sufficient quantity of active gland substance is not left in situ.

As early as 1818 Ch. Jong and in 1833 Langenbeck observed spasms occur after the total excision of the thyroid gland; in Billrot's clinic between 1870 and 1880 the disease was observed about forty times after operation.

The disease exhibits itself in tetanic spasms, somewhat resembling tetanus, which occur not only in the extremities, but also in the muscles of the larynx and diaphragm, soon causing death. The convulsions are of two grades of intensity, which may occur in the same case, the lighter ones occurring in the early stages, increasing in severity as the disease nears its termination. Sometimes the convulsions appear immediately after the operation, at others not till ten days later. Usually there are premonitory symptoms of an attack, consisting of a feeling of uneasiness and stiffness, with a weakness in the muscles of the forearms and the calves of the legs; rarely there are no premonitory symptoms, the attack coming on with great suddenness. In many cases it is possible to predict a tetanic condition before the first spasm, from the feeling of numbness, etc., and more especially from the Chvostek and Trousseau phenomena. The first consists in very rapid sucking movements, which are produced by light taps on the facial nerve as it leaves the parotid gland. The second and by far the most important of the two is that in a few minutes after pressure on an artery or nerve a convulsion of the part which they supply is produced. Chvostek's sign is so easily carried out, being without any danger or discomfort to the patient, that it should be always tried after total extirpation of the gland. Trousseau's sign is not without danger, as the muscle convulsions which it produces may be very severe. The convulsions usually begin in the calves of the legs and with a

feeling of numbness in the face; in light spasms the convulsions are usually confined to the upper extremities, seldom occurring in the lower extremities at the same time; the position of the joints of the hand and fingers suggest irritation of the ulnar nerve, the arm is slightly bent at the elbow and flexed toward the ulnar side, the



FIG. 31.—Cachexia strumipriva in a girl 26 years old. (v. Bruns.)

fingers bent at the metacarpophalangeal joint, the interphalangeal joint is straight and the thumb in the palm of the hand, as in the typical writer's or mid-wife's hand. This is the most common position; in other cases the fingers are extended wide apart or the fist is closed, with the thumbs between the index and middle finger. The muscles of the forearm are hard and tense to the touch; it is difficult to move the joints of the hand or fingers

during the spasm; they immediately return to their former position. In the majority of cases the spasms of the upper extremity are accompanied by the lower, which consist of stretching of the hip and knee with plantar flexion, the tendons drawn to the sole of the foot, while the severest strain is on the calves. The expression of the face shows intense pain, there is profuse sweating, the temperature may rise a little, the pulse rate be increased. The spasms last from two or three minutes to a quarter of an hour or more and occur several times in the day or one each day, or on alternate days. The sensorium is always free. Sometimes there is edematous swelling of the extremities.

The severer forms, which usually begin with a light spasm and slowly or rapidly progress in intensity, may last in spite of medication for days with hardly any appreciable break. In these cases there is also contraction of the muscles of the face, they become fixed, the mouth resembling that of a fish. The abdominal muscles are also severely contracted, the recti standing out like strands of steel. The tonic spasms of the back often produce opisthotonos. When the spasms attack the diaphragm the respiration comes to a standstill, in expiration followed by severe dyspnea. The contraction of the muscles of the neck produces cyanosis. The patients suffer from great pain as well as from air hunger, sometimes shrieking, in other cases this is impossible, owing to spasm of the muscles of the larynx, articulation may be possible at short quick intervals, when the same word may be repeated each time. Swallowing is also impossible, so that only small quantities of fluid can be given. As the end approaches the patient becomes comatose and the spasms cease, only to commence again when he is aroused from the coma. Death rarely supervenes during the height of the spasms, but hours or days after they have subsided.

The microscopical findings are negative, twice Weis



found slight infiltration of the gray matter of the anterior horn of the medulla.

From the experiments on the extirpation of the thyroid and parathyroid glands recorded above, it is probable that the tetanic convulsions after total excision of the gland are due to the parathyroids having been included in the tissue excised, especially as cases of tetany have occurred where there was apparently sufficient active thyroid tissue left in situ to prevent the patient suffering from athyroidia; in the latter case the parathyroids have either been injured before or during the operation or have been completely removed. It is probable that operative tetanic thyropriva will be very rarely seen in the future, surgeons being fully alive to the importance not only of leaving sufficient thyroid substance but also the parathyroids. Should a case occur the treatment consists in thyroid and parathyroid feeding, but the prognosis is very unfavorable.

Cachexia strumipriva is really a myxedema produced by the removal of the thyroid gland, either totally or partially, by operation. In 1867 Sick removed a goitre from a ten-year-old boy, who was at the time of the operation of average mentality; shortly after the operation the boy became stupid and gradually cretinic. In 1883 Riverdin and Kocher both published their observations of a cretinic condition supervening after removal of the gland.

The disease, unlike tetany, does not appear till sometimes weeks or months after the operation, and exhibits itself in a loss of mentality, in a chronic edema of the skin, and if the operation has been performed in youth the growth of both mind and body ceases from that time on. At first there is only apathy and loss of energy observed, but later there is a decided loss of intelligence, the memory becomes poor, finally progressing to a complete apathy, out of which it is impossible to arouse him.

Tetany is rarely present, but the sensibility is reduced. In some cases the mentality is not much affected though the skin changes occur, rendering the diagnosis easy.

The skin of the face becomes thickened, white, waxlike, rough and dry, the sweat and sebaceous glands ceasing to functionate; the hair becomes white and falls out, the expression and general appearance gives the impression of premature aging, the eyelids swell and bag. There is an edema of the extremities which does not pit on pressure, there is also a thickening of the skin in the gluteal region, while in the supraclavicular region there are swellings which resemble lipomata; the mucous membranes are thickened, the tongue and gums swollen, so that the patient speaks slowly and with difficulty.

The blood changes consist in reduction of the red corpuscles, which may fall as low as 2,000,000. There is also said to be a leucocytosis. The patient suffers from cold, complaining of feeling chilly even in warm rooms.

Should the operation have been performed in youth the patient ceases to grow in height; the growth in breadth increasing out of proportion, the genitalia cease to develop. The cause of the arrest of growth appears to be the arrest of the development of the long bones. In cases where the patient has lived into manhood, the epiphyses were found unaltered and the ends of the bones not ossified. The symptoms vary in degree from complete myxedema to slight symptoms which may be difficult to recognize.

The treatment of tetany and cachexia strumipriva consists in the administration of thyroid gland and in the former condition it seems probable that the addition of parathyroid gland would be of service.

Wounds of the thyroid seldom occur. Occasionally in cases of suicide, attempted murder, or during the operation for tracheotomy the gland may be wounded. In the

two former cases there is, besides the wounding of the gland, damage to the vessels, nerves and possibly trachea, at the same time.

The danger in these wounds of the thyroid is the hemorrhage, which may be very severe; if the trachea has been cut or the operation of tracheotomy performed, asphyxia may occur by the blood flowing into the trachea. Should the gland have been wounded there may follow a progressive cirrhotic condition, which may progress to a more or less pronounced myxedema.

In a case seen by the writer, a suicide in cutting across the trachea, wounded the thyroid slightly; on his recovery from the wound a band of scar tissue contracted the trachea, pressing on the gland, causing severe dyspnea. He was operated upon and the dyspnea ameliorated, the melancholia disappeared later and he was discharged. About six months after he returned to the hospital showing many of the symptoms of myxedema, yet suffering from acute mania. He was put upon thyroid treatment, making a very rapid and complete recovery.

## CHAPTER VII.

### THE THYROID IN INFECTIOUS DISEASES.

The thyroid gland is subject to congestion under the normal conditions of puberty, menstruation and pregnancy; at times the congestion becomes so severe as to produce dyspnea and asphyxia. This is, however, very rare. The patient notices a marked bilateral enlargement of the neck, usually accompanied with mental depression, an increased pulse rate and slight tremors. If the condition occurs at any of the above periods it will completely disappear in a few days of its own accord, or there may remain a slight permanent enlargement, which will increase at every succeeding period, progressing to a chronic goitre, often ending in degeneration of the gland and consequent myxedematous symptoms.

Should treatment be deemed necessary iodid of potassium or Lugol's solution in full doses will usually reduce the tumor in a few weeks. If there is danger of asphyxia partial excision of the gland should be resorted to in preference to tracheotomy.

In the acute infectious diseases the thyroid gland often suffers more or less severely and many cases of cretinism, infantilism and myxedema date from an acute infection.

The pathological anatomy in these cases has been studied by Roger, who has found that in spite of the diversity of the diseases, which include scarlet fever, diphtheria, typhoid fever, cerebrospinal meningitis, measles, smallpox and purulent peritonitis, there are a number of characteristics common to all.

To the naked eye the gland appears to be normal, but is increased both in size and weight. Taking the average

weight of the normal adult gland as 25 grms., he has found the weight above 30 grms., and as high as 71 grms. In these hypertrophied glands the microscopic changes are marked.

The color of the gland is altered from the normal yellowish tint to a red or violet shade, the parenchyma is uniformly red or brownish, marbled with violet. A part of the gland, however, may retain its normal color, it being not uncommon to find one lobe congested and changed in color while the other may be perfectly normal and even

the affected lobe may not be uniformly altered, the base being the portion most often affected.



FIG. 32.—Congestion of the thyroid.

The histological lesions are of considerable interest. The connective tissue is in general but little altered; sometimes, especially in infants, it contains an excess of nuclei, but never, either in the child or in adults, are the masses of leucocytes observed which are seen in the liver and other organs in infectious disease. On the first glance the impression is given that there is a marked increase

in connective tissue, which is due to the presence of the colloid substance within the vessels. It appears as if thick intravascular bands converged towards the vessels, but these bands are not formed from connective tissue. With a higher power it is seen that the fibres are eccentric and that the intermediate spaces are filled with a homogene-

ous substance, uniformly colored, giving the reactions of colloid substance dilating the lymphatic spaces. The whole appears like a network surrounding the vesicles. This condition exists in nearly every thyroid gland in infectious disease.

The alterations in the vessels are less acute, they are dilated and filled with red corpuscles, as are the capillaries. In a case of smallpox the red corpuscles had extravasated, mixing with the leucocytes and colloid, forming a magma without definite limit in the midst of which true thyroid cells could be distinguished, the hemorrhage had remained interstitial. In a case of diphtheria the blood had penetrated into the interior of the vesicles, but the lesion was limited and affected only a small portion of the parenchyma. Arteritis and phlebitis occur, the intima thickens, progressing into the interior of the vessel, producing thrombosis with more or less complete obstruction of the lumen. Periarteritis and periphlebitis are rare. The most interesting lesions are those of the parenchyma, the vesicles being altered in form, dimension and constitution, the colloid being sometimes altered in its essential qualities. Usually the vesicles are reduced in size, as the intravascular vessels are diluted by colloid, several of the acini may no longer contain colloid and their centre is occupied by cells in a state of disintegration. The connective tissue surrounding the vesicle is easily made out, but the lining cells have desquamated from the walls in many places, and are in the centre of the vesicle mixed with the colloid. The protoplasm of these cells is granular, the nucleus large, of irregular shape, staining badly with hematoxylin. Sometimes several cells are massed together in the centre of the vesicle, in the midst of which are the nuclei in degeneration. Other vesicles on the contrary contain a certain amount of normal colloid.

The colloid substance does not react to the stains as normally. Safranin instead of giving it a strong red only produces a faint rose color; sometimes it loses its affinity for eosin and remains yellow, to aurantium it fails to react normally, producing a dirty brown, very different from the characteristic light yellow. Occasionally certain vesicles, containing instead of colloid a mass of brownish granulations, fail to take eosin, but become green with thionin. Sometimes these granulations fill a whole vesicle or there may be only a small mass among the desquamated cells. They only exist among the glands, which are much altered.

When the lesions produced in the thyroid by the infectious diseases are very marked, the secretion of colloid either ceases or is replaced by granulations of abnormal reaction. The vesicles are uniformly filled with desquamated cells crowded together, which have large, clear protoplasm more rarely granulated. The walls of the vesicles have degenerated and are no longer able to contain the colloid substance.

The pathology of the parathyroids in infectious diseases has so far received but little attention. Roger examined them in one case of scarlet fever and in a case of diphtheria. In the case of a woman dying of scarlet fever, where the changes in the thyroid were comparatively slight, the four parathyroids showed marked lesions. The spaces in the connective tissue instead of being exactly filled with epithelium, as in normal glands, were half empty. The cells were not dispersed regularly on the base membrane, and were massed in the centre of the spaces. They consisted of granular protoplasm with ill-defined limits. The nucleus stained well. These lesions were found in various parts of the gland; at the same time there was much healthy tissue. In the case of diphtheria they found the same lesions.

The above are the lesions found to a greater or less

extent in all infectious diseases; there are, however, some variations distinctive of the different infections.

In scarlet fever the gland suffers very severely. In 15 cases examined by Roger only two were found to be about normal, one being that of a child of 16 months, the other in a woman of 30, but in the latter the parathyroids were markedly abnormal. Congestion was always present; there was no hemorrhage. The walls of the vessels were affected. In two cases endarteritis thrombus was observed. Hypersecretion of the colloid was observed in nearly every case, twice the colloid was altered, reacting abnormally to the staining reagents.

In measles the gland resists the disease better than in scarlet fever. In only half of the glands examined was there any abnormality observed.

In smallpox, in the gland of the one case examined, the lesions were very severe. The gland was hypertrophied and much congested. This case differed from scarlet fever in the presence of small parenchymatous hemorrhages, at the same time the colloid was abnormal, being brown and granular.

In diphtheria the hypersecretion is less marked than in scarlet fever, the vesicles contain numbers of desquamated cells and colloid substance is usually altered; rarely is there any hemorrhage.

The intensity of the lesions does not appear to depend on the duration of the disease nor is it affected by intercurrent diseases. Out of the 15 cases examined, four succumbed to streptococcus complications, but showed no complication of the lesions.

In measles it is somewhat difficult to say what are the lesions of the gland in an uncomplicated case, as death from measles is rare, the complications usually being bronchopneumonia, rarely meningitis, gangrene of the pharynx and purulent coryza.



Garnier made some experiments on animals, inoculating them either under the skin or in the veins, and others in the thyroid arteries; under the latter condition the results were very instructive. He used the staphylococcus aureus, which produced a diffuse thyroiditis; if the cultures were very virulent they produced parenchymatous lesions; if attenuated, interstitial lesions. In the first case the vesicles were reduced in size, they contained pale colloid, the epithelial cells were swollen, their protoplasm staining uniformly, and in places they appeared as fused together in a mass, the nucleus was swollen, staining badly, the vessels gorged with blood, the connective tissue apparently normal. If the culture used was extremely virulent there were destructive lesions; with death of the cells the vesicle disrupted, the colloid filling the lymph spaces.

If an attenuated culture was injected there was arteritis; in the vesicles were masses of leucocytes, in the centre of which were degenerated epithelial cells.

The experiments with the typhoid bacillus produced the same diverse anatomical lesions, but more diffuse. With very virulent cultures hemorrhagic thyroiditis occurred. With less virulent cultures there was epithelial degeneration, capillary congestion and endarteritis. When the animals were allowed to survive sclerosis occurred in the form of bands of connective tissue, which divided the gland into segments. The vesicles appeared to be normal, but their walls were much thickened. There was also a certain quantity of endarteritis and periarteritis.

Toni experimented on the same lines with the pneumococcus, the typhoid bacillus and anthrax. He used less virulent cultures than Garnier and therefore did not obtain such marked results, but the same in kind. These experiments show that the infectious diseases produce certain lesions in the gland which vary according to the intensity of the infection.

Suppurative thyroiditis is not uncommon in the infectious diseases, and hemorrhagic thyroiditis is rare, occurring most often in smallpox. Sclerosis of the thyroid may occur as the result of any of the acute infectious diseases, and also in tuberculosis and syphilis, which accounts for the numerous cases of myxedema and infantilism which occur after a severe illness. The symptoms of myxedema may not occur for months or years after the disease, the sclerosis progressing slowly.

When the inoculations were made at a distance from the gland, there were but slight pathological changes in the glands. The staphylococcus, the typhoid bacillus and anthrax produced no lesion that could be detected, the streptococcus, however, produced lesions resembling those described as occurring in man.

By injection of diphtheritic toxin into a guinea pig Roger observed lesions in the gland resembling those occurring in man. The colloid substance leaves the alveoli, entering the lymphatics; at times it is so abundant as to entirely mask the vesicles, and in the lakes that form there are epithelial cells. At other points the cells desquamate into the middle of the vesicles. All the colloid passes into the vessels but preserves its normal characteristics.

The tetanus toxin produced rather different results, the lesions were less marked and consisted principally in a slight hypersecretion. In one case which developed slowly the colloid was granular and yellow, taking the stain poorly.

The effect of the inoculations of cultures and of toxins upon the gland seems to resemble very much the action of nitrate of pilocarpin and iodid in producing a hypersecretion which flows into and gorges the lymphatics, dilating the vesicles, and there appears but one vast mass of colloid scattered irregularly, among which are rows of nuclei, the cells having desquamated and filled the cavity

of the vesicles, their nuclei staining badly, showing irregular outlines, the colloid remains normal, while in the infectious diseases, although the anatomical lesions are the same, the colloid is evidently chemically changed, so that while there is a hypersecretion there may also be "dys-thyroidation" which may amount to a suppression of function of the gland.

It follows, therefore, that during the course of infectious diseases there are secretory troubles in the thyroid gland as well as in the other glands of the body, a period of superactivity followed by a diminution or alteration of function, as the liver secretes abnormal pigments so the thyroid secretes abnormal colloid substance.

Usually the lesions are slight and are quickly repaired, but it may not always be so, pathological conditions may continue to exist and may be progressive, producing partial or complete loss of function, accompanied with the symptoms of hypo- and athyroidea.

## CHAPTER VIII.

### ACUTE THYROIDITIS.

Acute inflammations of the thyroid were observed in the middle of the seventeenth century, terminating as suppurative goitres. Libert in 1862 and Bauchet in 1877 wrote monographs on the subject which are classical in France.

Acute thyroiditis is always due to infection, a predisposing cause being a goitrous condition of the gland which then becomes cystic. The disease occurs most frequently in women, usually between the ages of 20 and 40, occasionally in children, and very rarely over 50 years of age.

Among the causes of susceptibility besides goitre are trauma and cold. The trauma may be due to pressure, such as strangulation. When the inflammation is preceded or accompanied by a cold it is due to an infection, usually streptococci from a pharyngitis. The gland is liable to infection from its circulation, a venous congestion being easily produced by shouting or long talking, during labor, and in various other ways; it also may occur at the climacteric. Nearly always, if not always, thyroiditis is a secondary lesion during the course of an infectious disease, among the most common being typhoid fever. The pus in the gland has been found to contain the bacillus of Eberth by Tavel, Kocher and many others, either in pure culture or associated with other organisms. Some cases can be attributed to a secondary pyemia, it having been observed in purulent infections, posttraumatic, postoperative or other suppurative lesions. It is, however, in puerperal infection that the disease is most common, the organism being usually a streptococcus.

The diseases which may produce acute thyroiditis are the eruptive fevers, scarlet fever, measles, smallpox, erysipelas, diphtheria, influenza, pneumonia, articular rheumatism, and particularly malaria. It has also been observed to accompany or follow bronchitis, pharyngitis and coryza. In diseases of the digestive tract it has been observed in catarrh of the stomach when the bacillus streptococcus lanceolatus was isolated, in acute enteritis, and in proctitis when the bacillus coli communis was found. The staphylococcus pyogenes was found in a gland during a case of osteomyelitis.

The symptoms vary with the accompanying disease. Should there be a primary infection of the gland there would be the chills, fever, malaise and headache common to all infections, followed by the more distinctive symptoms of pain felt in the region of the gland, which is increased on pressure, localized in the majority of cases in one lobe, usually the right; the pain increases on movement, especially in extension, causing the patient to carry his head thrust forward and bent downward so as to relax the muscles as much as possible; sometimes supporting the chin with the hand; often the pain radiates to the ears and neck. At the end of the first or second day the enlarged lobe usually becomes palpable, very rarely the tumor is confined to the isthmus.

On palpation the tumor is found to be attached to the deep tissues moving up and down on deglutition, it feels at first hard and perhaps elastic; there may be displacement of the trachea, which becomes compressed should the tumor reach a large size, causing dyspnea, which may require prompt surgical interference.

The compression of the vessels causes distention of the superficial veins, headache, ringing in the ears, vertigo, and sometimes epistaxis. Pressure on the pneumogastric nerve may also add to the dyspnea. The patient is an-

noyed by a dry cough, accompanied by a slight expectoration streaked with blood, or there may be true hemoptysis. The voice is rough, harsh and thick, speech slow and difficult, sometimes the aphonia is absolute. The respiration becomes painful and wheezy. There may be pressure on the esophagus, or pressure on the nerves, producing painful and difficult deglutition, with a feeling as if there were a foreign body at the back of the throat; vomiting may be very severe.

The irritation of the various nerves compressed by the goitre may cause a number of very varied symptoms, such as pains in various regions of the body, formications and paralysis of the hands. This latter symptom is said to be occasionally produced by a functional trouble of the gland.

Thyroiditis may terminate by resolution, by suppuration or by gangrene. In the first case the symptoms increase for three or four days, then remain stationary for some days, characterized by fever with matutinal remissions with a more or less serious condition for five or six days. At the end of this time the gland, which has been steadily growing, commences to diminish in volume, the tumor disappearing in about twenty days. Sometimes there is a return of the swelling after a few days. In many cases the gland never returns to its former volume, remaining permanently enlarged.

Suppuration occurs in about 60 to 70 per cent of the cases, as in all cases of infection there are chills, fever, malaise, headache, etc., but there is also a change in the character of the pain, which becomes lancinating; the skin over the gland, which has up to this time remained normal or slightly streaked with the engorged veins, becomes hot and red, losing its mobility over the deeper tissues. The cervical region becomes enlarged, accompanied by an edema in the substernal region as well as in the upper portion of the thorax.

Fluctuation is always late in appearing and is difficult to detect, owing to the depth of the tumor, and is not of such symptomatic value as the discolorations and edema of the neck. Exploration by puncture will usually have to be resorted to if it is necessary to operate early in the disease. As the pus is very thick and the tumor perhaps a long distance from the surface, even a negative result cannot be relied on.

If the abscess is left alone it usually opens externally; the skin becomes red and taut before perforation, the pus is either a serous liquid, fetid, bloody or contains gas. Usually cicatrization is rapid, at others a fistula may remain for a month or even years. The abscess may perforate into the larynx, trachea and esophagus, or into the surrounding tissue; in the latter case the condition becomes very grave, sinus forming in the direction of the face, the neck, the clavicles or the pleura.

Gangrenous thyroiditis is rare, there being only eight cases on record and is of very grave prognosis. The condition develops rapidly, the gas forming under the skin causes distention which rapidly breaks down, leaving a large opening in which the carotid arteries and the arch of the aorta may be visible.

A rheumatismal thyroiditis occurs during an acute attack of rheumatism, never suppurates, and is characterized by a mobile and fugitive congestion, often developing with great rapidity within a few hours and disappearing in the same manner. The pain in the region of the gland is very intense, causing the patient to thrust his head forward to support his chin with his hand. It rarely lasts more than three or four days, though it may return or alternate with other manifestations; the neck may remain permanently enlarged.

The thyroiditis of mumps is somewhat similar in its character to that of rheumatism, but is extremely rare and has not been observed to suppurate.

The thyroiditis of grippe may attain the size of a hen's egg, it recedes about the sixth day and does not suppurate. The symptoms which it produces are those of hyperthyroidism, viz: vertigo, palpitations, tachycardia, tremors, etc.

The thyroiditis of malaria rarely suppurates, except in goitrous cases.

The thyroiditis of typhoid is the most frequent form of secondary acute thyroiditis, usually appearing at the commencement of convalescence, and is probably a local infection from the bacillus of the disease. When it occurs during convalescence there is a rise in temperature with a hyperleucocytosis instead of the hypoleucocytosis of the typhoid fever. Suppuration is frequent, occurring in about 50 per cent. Generally the course is favorable with rapid cure.

Pyemic thyroiditis is a much more grave disease than the other forms, as the points of infection are scattered through the gland, rendering the probabilities of a favorable termination very remote.

The pathological anatomy of this condition requires only a short description. In non-suppurative conditions the tissue is much congested, of a dark red color, dotted with small hemorrhages. Under the microscope pigment degeneration of the cells is found, congestion of the capillaries and the colloid infiltrated into the interstitial tissue.

The suppuration is generally in the bands of connective tissue, looking under the microscope like small miliary abscesses.

The diagnosis of acute thyroiditis presents but little difficulty. The treatment depends upon the cause, it being directed to the general infection. A purgative to deplete the system has often a good effect in reducing the tumor, external application of belladonna ointment or of hot compresses may be of service. If there is suppuration the abscess should be opened as soon as it can be definitely defined, usually it will heal up rapidly.



## TUBERCULOSIS OF THE THYROID GLAND.

The thyroid gland is subject to two kinds of lesions in tuberculosis; it may be invaded by the tubercle bacilli with the development of the typical granulations, or the toxins formed in the general system may produce sclerosis and consequent loss of function. Tubercle formation in the gland is rare, on the contrary the sclerosis of the gland is always present.

Previous to Lebert's work in 1862 the pathological research on the thyroid had been principally confined to goitre. The latter investigated and found miliary tubercles in the gland of a woman 25 years of age. Virchow reported a case of caseous tubercle, which was followed shortly after by reports of cases by Fraenkel, Bruns, Rolleston and others. Chiari found tubercles in the thyroid in 4 per cent of his cases. Weigert found tubercles in the thyroid of all of the eleven cases of miliary tuberculosis that he examined; others have not found them so frequently. They are more common in young persons and children than in older patients.

In certain tubercular patients the tubercles produced by the disease cause a swelling of the gland, which may be so great as to cause discomfort to the patient, occasionally compressing the neighboring organs, producing the various symptoms already described. Fumolard describes a form of this infection under the title of follicular thyroiditis, being subacute in its progress, characterized by successive infections, producing fistulous openings.

In the second form the gland contains caseous nodules, but is not so enlarged as to press on the neighboring organs. In Virchow's case the nodule was about the size of a cherry. In a case of Grasset and Estor's the left lobe was double the normal size, hard, covered with small tumors, the size of a lentil, on the anterior and superior surface, attached to the gland by a pedicle. Rolleston re-

ported a case where there was a caseous mass in the gland with an abscess having two orifices opening into the esophagus, one the size of a ten-cent piece, the other much smaller.

The third form corresponds to miliary tuberculosis, the tuberculous granulations are distributed on the surface and in the parenchyma of the gland, the granulations are yellow and easily distinguished with the naked eye and of about the size of a millet seed. Sometimes the granulations are very small and can only be recognized by the aid of the microscope, the gland appearing normal on macroscopical examination and is not increased in volume.

In the neighborhood of the tubercle the gland is profoundly altered, the position of the vesicles is indicated by the granular cells, which are in circular or elliptical groups, but poorly stained. The cavity of the vesicles does not contain colloid but a few fibrils surrounding the epithelial cells. Between the vesicles there is an increase of fibrous tissue, enclosing numbers of fixed proliferated cells.



FIG. 33.—Tuberculosis of Thyroid.

On injecting cultures of the tubercle bacilli into the thyroid gland of animals by way of the thyroid artery granulations were produced of the same type as those found in man. The first effect of the bacillus or its toxin is to cause degeneration of the cells. As the most highly differentiated elements are always least resistant, the vesicular epithelium was the first attacked. If the cultures were very virulent or a large quantity was injected, and the organism like that of the guinea pig very susceptible,

this reaction is not marked. If the action is less energetic or the resistance greater the reaction occurs. As soon as infection has become general, the toxins formed in the other parts of the body are brought to the gland by the circulation and sclerotic lesions commence. If, on the other hand, the bacilli penetrate and find a nidus in the gland the quantity of toxin formed produces a more intense reaction and tubercular granulations.

Sclerosis of the thyroid is almost invariably found in tuberculous disease and has been described by Garnier as occurring in eleven out of twelve cases examined. Charin and Nathan Lerrier showed that it exists in the newly-born of tuberculous mothers. In a case described by Roger, where the gland was not sclerotic, the gland weighed 90 grms., being three times larger than normal, containing neither granulations nor sclerosis; the vesicles were filled with colloid and the cells apparently normal. It would appear that the existence of a goitre had tended to preserve the gland from the action of the toxin.

It is difficult to determine what symptoms in phthisis, if any, are due to sclerosis of the thyroid. The tachycardia, so often noticed in the early stages of tuberculosis, may be produced by a superactivity preceding the destruction of the tissue and sclerosis. The sclerosis of the gland must necessarily, if going far enough, produce loss of function of the gland and may account for some of the many varied symptoms which occur in the disease. The fact that patients who recover from tuberculosis often become very stout may be due to a hypothyroidea produced by a sclerotic condition of the gland.

Gautier and Bourcet have shown that the iodine and arsenic disappear from the gland in tuberculosis, which may account for the troubles of the skin and of the menstrual function and he claims to have removed these symptoms

by the administration of cacodylate of soda combined with very small quantities of iodine.

A macroscopic examination of the gland shows that it is much reduced in size, weighing as low as 8 grms., the surface is paler than normal on section, the tissue is irregularly colored, partly yellow and partly pink; the gland is harder than normal and in advanced cases the bands of connective tissue can be distinctly seen.

The microscopic examination shows either a pure sclerosis or the latter associated with parenchymatous alterations. The most common lesion is atrophic sclerosis while more rarely there is a hypertrophic sclerosis.

In trophic sclerosis the connective tissue may be diffuse and irregular, at other times regularly distributed, forming geometrical figures more or less typical. In the first case the tissue is abundant, surrounding the vessels in concentric circles, giving the idea of a lobular formation. The vesicles are compressed between the bands and may be empty of colloid. The external walls of the arteries are thickened, often accompanied by endarteritis, the lumen is decreased and sometimes obliterated. In the veins the lesions are usually less marked.

The parenchyma is little changed, the vesicles appearing normal, but in certain parts the gland shows a condition of functional hyperactivity. The islands of vesicles formed by the bands of connective tissue secrete actively, the cellular detritus infiltrates into the vesicles while occasionally the colloid appears in the lymph spaces. Sometimes the sclerosis is accompanied by the formation of abnormal colloid.

In hypertrophic sclerosis the gland is enlarged and may weigh as much as 52 grms., the sclerosis is irregularly distributed, and in the neighborhood of the larger vessels are large islands of vesicles. The parenchyma is in a state of active cell proliferation, the irritation of the toxin

has evidently produced an abnormal multiplication of the elements, the cells appearing healthy but of small secretory power. It is probable that this hypertrophy is the first effect of the action of the toxins which progresses to atrophy of the gland.

## CHAPTER IX.

### SYPHILIS OF THE THYROID.

The thyroid gland is sometimes the seat of a syphilitic inflammation in secondaries or tertiaries, the gland becoming so large as to cause dyspnea, but this is exceptional. Wölfler records a case where the thyroid was found to contain a gumma the size of a fist. Fraenkel reports a case which died of syphilis of the trachea, lungs and liver. At the autopsy it was found that between the isthmus and the right lobe there was a mass of yellow substance which, on microscopical examination, proved to have developed in the interfollicular tissue and had compressed and invaded the parenchyma of the gland. The lesion is differentiated from tubercle by the absence of giant cells and degeneration.

Hereditary syphilis is occasionally found in the thyroid gland. Demme found small gummas in five cases. Fürst records a case of a child born of a syphilitic mother who presented none of the typical symptoms but had a large goitre which he considered to be of syphilitic origin.

Garnier studied the glands of five newly-born syphilitic children. In only one case was the gland healthy. The lesions were remarkable as being diametrically opposite to those found in the adult; the colloid substance instead of being increased was reduced or absent. The vesicles were uniformly full of cells, the capillaries dilated, small hemorrhagic points scattered through the gland and at the same time focuses of cellular degeneration. These lesions are not confined to hereditary syphilis but occur more or less marked in all cases of infection of the fetus. These lesions are of importance as they may account for

many of the troubles occurring in the development of the child.

Abraham reports three cases of women who developed exophthalmic goitre, the first five months after the primary lesion, the second during the height of secondary infection, and the third two years after infection, all of whom were cured by antisiphilitic treatment.

Faisans and Audistère reported a case with both gonorrheal and syphilitic infection, who developed a pseudomyxedema in which the myxedematous symptoms were not affected by mercurial treatment but disappeared under thyroid feeding.

Köhler has reported cases of myxedema following syphilis, and Demme has observed symptoms of Basedow's disease to occur.

#### CANCER OF THE THYROID.

Cancer of the thyroid gland is rare, occurring only 19 times in 10,000 cases and very rarely except in glands which are goitrous.\* It usually appears between the fortieth and fiftieth year. Schuh observed it in a young man of 16, and Demme in a child. Traumatism is probably a factor and Kauffman suggests pregnancy as favoring its development, owing to the congestion of the gland during that period.

Usually the tumor is unilateral, but may affect both lobes; the enlargement may be as large as a hen's egg or even greater, being sometimes hard, at others soft.

Cancer of the thyroid has a tendency to invade the neighboring tissue; the trachea, the larynx and the esophagus are compressed by the neoplasm, causing ulceration and perforation.

Thyroid cancer is a tubular epithelioma characterized by the development of narrow spaces filled with polygonal cells, there being many grades between an adenoma and a true cancer.

The tumor generally develops in a preëxisting goitre, probably remaining latent for some time, then developing rapidly, the patient dying in five or six months. During the course of the disease many of the symptoms of Basedow's disease occur, at other times the patient complains of heat and of sudden congestions of the head, accom-



FIG. 34.—Columnar celled Carcinoma of Thyroid Gland.

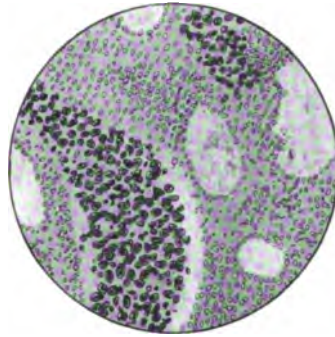


FIG. 35.—Adeno Carcinoma of Thyroid Gland.

panied occasionally by a temperature of 38 or 39 degrees C.; also the urine shows increased nitrogen elimination, albumin or sugar as in Basedow's disease. There are no premonitory symptoms, the patient seeking advice on account of the rapid increase in size of the existing goitre.

Owing to the rapidity of the growth of the tumor and its invasion of the neighboring organs, the patient suffers from great functional disturbance, the pain radiates to the lower jaw, the teeth, the neck, the temples, the ears or towards the hands; violent pains of the stomach are not uncommon, probably due to pressure on the pneumogastric nerve. Compression of the trachea or the recurrent laryngeals causes some dyspnea and strident inspiration. Should the esophagus be attacked deglutition is difficult and painful, sometimes impossible. When there is thrombosis the superficial veins of the skin are dilated, accompanied by edema of the presternal region.



Rarely does the patient die from the cachexia but by a complication, such as the extension of the disease to the lungs which can be recognized by the blood in the sputum or by a bronchopneumonia or suffocation. Ulceration of the carotids, obliteration of the jugular vein, ulceration of the trachea, perforation of the esophagus and ulceration of the left carotid all occurred in a case reported by Poumet.

The diagnosis is difficult, exploration with the needle is the most likely to give satisfactory results.

The prognosis is very bad, as medicinal treatment is of no avail, and operation is hardly likely to give good results, considering that in all probability the whole of the gland will have to be removed and that the neighboring tissues are more or less involved.

#### SARCOMA OF THE THYROID.

Sarcoma of the thyroid is rare and, curiously, seems to be more common in men than in women. It usually develops between the ages of 50 and 60 years. It differs from cancer in that it attacks healthy glands more often than those affected with goitre. It may grow to a great size, having a glossy surface and being of a soft consistency. It often contains cysts or calcareous deposits. Pulsating sarcomas have been observed.

The tumor develops in the intervesicular connective tissue and may be either spindle celled or round celled. The evolution is rapid, producing the symptoms of pressure, etc. The patient usually succumbs within a year of the development of the disease. The tumor is usually accompanied by the symptoms of Basedow's disease. The treatment is extirpation but the prognosis is grave.

#### HYDATID CYSTS OF THE THYROID.

Hydatid cysts of the thyroid are very rare and can only be diagnosed by exploration. The syringe will contain

a clear liquid, sometimes purulent. The diagnosis can be made with the microscope and by chemical examination for succinic acid.

The treatment consists in opening up the cyst or injecting iodine, when it heals easily; should the cyst break into the trachea the prognosis is very grave.

## CHAPTER X.

### CRETINISM.

Myxedema, a disease the result of absence or loss of function of the thyroid gland, either congenital or acquired, was first described in 1873 by Sir William Gull, in a paper read before the London Medical Society, entitled "A Cretinoid Condition Supervening in Adult Life," in which he describes the three principal symptoms as tumefaction of the skin, a general cachexia and a cretinoid condition. Four years later Dr. Ord published observations on two similar cases, with an autopsy as well as a chemical examination of the skin, giving the disease the name of myxedema, since which time the literature on the subject has become very voluminous, giving a complete picture of the disease and establishing its symptomatology.

Myxedema is subdivided into cretinism (endemic and sporadic), which are cases of congenital absence or loss of function of the gland occurring during the first year of postnatal life. Infantilism is a term applied when the thyroid function is partially or completely lost before puberty. The term myxedema is applied to those cases where the function is lost during adult life. Between the normal condition of the gland and its complete or almost complete cessation of function, there are necessarily an infinite number of degrees, producing various symptoms which it is of great importance to recognize as pointing to a possible relief by thyroid feeding and which are classified as masked myxedema. There is yet another form of infantilism known as "Type Loraine" which appears to be only partially due to loss of function of the gland. These various forms have one etiological lesion common

to all, viz: the loss of function of the thyroid gland, the differences being due to the age at which the disease occurs and the amount of functionation lost.

Endemic cretinism occurs in districts where goitre is endemic and almost invariably in the children of goitrous parentage; 75 per cent of these cretins are goitrous.



FIG. 36.—Cretin with goitre. (v. Bruns.)

There is no reason to suppose that cases with the same etiology as the sporadic form may not occur in goitrous districts, but the very large number of cretins in the affected districts is positive proof that a connection exists between endemic goitre and endemic cretinism. Occasionally a child is born with a small goitre and very rarely the goitre may be so large as to impede delivery; in these rare cases it is reasonable to suppose that there is an an-

tenatal infection of the fetus through the mother. In by far the largest number of cases, however, the goitre does not appear till the second year of life, that is after weaning, when the infection is presumably postnatal. Endemic goitre rarely produces myxedema in the adult, but it seems as if when the goitre occurs in early childhood



FIG. 37.—Cretin with goitre. (v. Mikulicz.)

the gland ceases to functionate, producing the typical symptoms. In the 25 per cent of cases which have no goitre but simply an atrophy or congenital absence of the gland it is evident that the condition cannot be due to either ante- or postnatal infection, with the contagium vivum of endemic goitre, and it is presumable that they are the result of the same etiological factors which produce sporadic cretinism.

The etiology of sporadic cretinism is by no means definitely settled; a certain number of cases may be due to the morphological absence of the thyroid gland, but such a *lusus naturæ* must be very rare. In the previous chapter on thyroiditis it was shown that syphilis and tuberculosis in the mother produce a hypothyroidea in the child and it is probable that other diseases, such as rheumatism, may have the same effect. Alcoholism in the parents, and especially if one or both were under the influence of liquor at the time of coition, has been accused. Fletcher ascribes two of his cases to this cause and other writers about 15 per cent of all cases. In Scotland the first-born was often feeble-minded and known as a "daft callant," which was popularly supposed to be due to the intoxication of the parents, the wedding festivities being often prolonged for several days after the ceremony, during which it was customary for the groom and often the bride to drink very freely of the national beverage. Consanguinity of the parents, impressions received during pregnancy and prolonged labor have also been cited as causes, but are probably merely coincidences.

The infectious diseases of the mother which have been observed as associated with cretinism in the child are



FIG. 38.—Cretin, 22 years old.  
(v. Wagner.)

tuberculosis, erysipelas, acute articular rheumatism, malaria and influenza, which are among the diseases described in the chapter on thyroiditis as producing pathological conditions of the gland. That the specific organism of these diseases should pass the healthy placenta and infect the fetus is improbable, but the toxins produced by



FIG. 39.—Cretin. (v. Wagner.)

them in the maternal circulation will certainly circulate in the fetus and possibly produce disease of the gland. These conditions will account for a certain number of cases, but some other etiological cause must be invoked for the majority.

In the chapter on the physiological experiments on the thyroid gland attention was drawn to the experiments of Halstead and others, who found that in the case of a bitch who had had two-thirds of her thyroid gland removed and who was impregnated by an unoperated dog she produced puppies with thyroid glands twelve times larger than normal. This experiment has since been repeated by Edmunds with the same results, showing that nature compensated for the absence of the thyroid secretion in the mother by stimulating the growth of the gland in the pups. It is probable that the reverse would occur, viz: that should the mother have an excess of thyroid secretion the gland in the young would not be developed and consequently the child would show cretinic symptoms after weaning, as up to that time it would receive a certain amount of the maternal thyroid secretion with the milk. In these cases the child would be a cretin, or should the

gland develop to a certain extent the symptoms would decrease in proportion to the development of the gland.

The occurrence of a cretinic condition without goitre, where goitre is endemic, suggests that the parenchymatous increase of the maternal gland, in conjunction with the normal hypersecretion of pregnancy, prevents the development of the fetal gland. The same reasoning will account for cases of sporadic cretinism, should the maternal gland be hyperexcited during pregnancy from any cause, then the fetal gland would fail to develop.

In support of this theory the following cases have been observed:

A lady who when first seen was between 50 and 60 years of age, suffering from a large bilateral goitre, with tremors, tachycardia and great depression, giving a history of being the mother of two girls and five boys, the goitre having begun to develop after her third pregnancy, and to have steadily progressed. The first four children were normal, the two girls were feeble-minded and died young, while the youngest boy, though mentally up to the average, weighed at 19 years of age 340 pounds. Another case was that of a woman who had a goitre, two of whose sons were feeble-minded and one of the daughters developed a melancholia at her second pregnancy, recovering under thyroid treatment. A third case is that of a woman who while pregnant with her youngest child developed a large parenchymatous goitre which disappeared a year or so after the birth of the child which was a typical cretin.

In the majority of cases of sporadic cretinism the disease of the gland can be traced to some acute postnatal infection which, producing a thyroiditis, arrested the development or partially destroyed the gland. It is by no means uncommon to get a history of the child having developed normally, both mentally and physically, till a few months after some sickness, from which time it has

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ceased to grow and the symptoms of cretinism to appear. The older the child at the time of the arrest of the thyroid function the more incomplete are the symptoms and the more difficult to trace their true cause.

The etiology of infantilism is the same as that of cretinism, except that it is probably never congenital, the lesion of the thyroid only taking place after infancy, the function of the gland being decreased and not entirely destroyed.

In myxedema in the adult the cause is the same, being a progressive arrest of function of the thyroid gland, the result of some disease or traumatism. Women are much more liable to this disease than men, the proportion being



FIG. 40.—Acute thyroiditis.

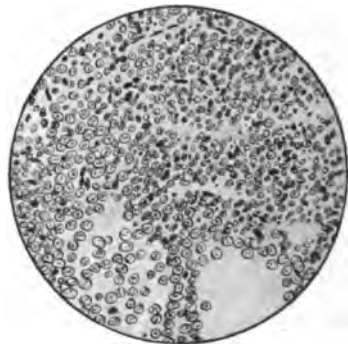


FIG. 41.—Suppurative struma of Thyroid gland.

about five to one, while in cretinism and infantilism the sexes are about equal. The susceptibility of women to this disease is no doubt the result of the strain thrown upon the gland by menstruation and pregnancy, the hyperactivity producing cell fatigue with a resulting atrophy. Hun and Prudden state that 64 married women with myxedema had 300 children and 29 abortions, and probably not all the abortions were admitted by the patients; but of 78 patients there were only 14 unmarried.

*Pathology.*—The indispensable lesion necessary to produce myxedema in any of its forms is an abnormality of the thyroid gland involving loss of function. Formerly the absence or pathological condition of the gland was regarded as accidental and not connected with the symptoms, but since the work of Gull, Ord, Schiff, Riverdin, and Kocher it has been recognized as the essential cause of the disease. The British commission on myxedema declared in 1884 that there was but one constant anatomical lesion in myxedema, the atrophy or abolition of function of the thyroid gland.

The abolition of function may be due to degeneration (goitre) or to atrophic sclerosis. Bramwell describes 44 cases of myxedema with 10 autopsies, in 9 of which no trace of the thyroid could be found and in the tenth the lobe was the seat of a tumor, which was either congenital or followed some infectious disease. In many cases the thyroid is represented by a mass of connective or of adipose tissue, the thyroid arteries being absent. In endemic cretinism 25 per cent of the cases show no trace of gland tissue, it being replaced by connective tissue; in the other 75 per cent the secretion is suppressed or perverted, due to a degeneration of the gland.

Virchow claimed that the mental deficiency in cretinism was due to premature ossification of the sphenobasilar bone, preventing the elongation of the base of the skull; others contended that the pressure of the goitre on the carotid arteries prevented a sufficient blood supply to the brain, and that the nongoitrous cases were due to insufficient cerebral circulation, from narrowing of the cranial foramina and other causes. Malcarné counted the lamellæ of the cerebellum and found only 300 instead of the normal 600; this observation was confirmed by others.

Ord, Virchow and Horsley examined the tissues microscopically and failed to find any trace of acini or of thyroid

cells, only a mass of connective tissue occupying the position of the gland. Stilling found the same condition and also the absence of the thyroid artery. Langhans suggested a process of interstitial inflammation of the gland with infiltration of the embryonic cells, absolutely compar-



FIG. 42.—Atrophic gland from a case of myxedema.

able with cirrhosis of the liver, the sclerotic tissue developing little by little, the vessels succumbing to endarteritis obliterans, the acini atrophying and disappearing. The British commission decided that the inflammation commenced in the parietal vessels, infiltrating the embryonic cells, which inflammation was accompanied by a proliferation of the endothelium, destroying the vessel walls. Under these conditions the epithelium of the acini proliferate, the connective tissue of the gland and the parietes of the acini become congested with embryonic cells which slowly transform into sclerotic tissue.

The sclerosis little by little stifles the glandular tissue, which takes on the appearance of islets, which gradually disappear; in short, there is an atrophy from interstitial inflammation which develops slowly toward a final sclerosis and thus to the suppression of the function of the gland. Coulon examined six cases and found that in no case was the thyroid entirely absent, but that there were tissue and cytological changes, which showed that the gland had almost, if not entirely, ceased to functionate, the acini being very few and small, apparently containing little or no colloid, while there was a great

increase of connective tissue. Other investigators have invariably found little or no normal tissue in the gland.

In cretins persistent thymus is not uncommon, the hypophysis cerebri is sometimes enlarged, sometimes atrophied. An observation of great interest is that the thyroid can be atrophied in cases when the mentality is nearly normal, though the physical condition may be distinctly cretinic. This observation and the results of physiological experiments with extirpation of the thyroid and parathyroids has led Brissaud to advance the theory that the thyroid gland has to do with the physical and the parathyroids with the mental development. Murray is of opinion that the parathyroids have to do with the nervous symptoms and the thyroid with the nutrition and assimilation.



FIG. 43.—Myxedematous gland.

Coulon points out that in the lower type of cretins the small amount of colloid present is of such a consistency as to be unable to pass into the lymphatics while in the higher types the colloid is mere fluid.

The skin is in a thickened pseudoedematous condition; there is hypertrophy of the connective tissue with atrophy of the sebaceous sudoriferous glands and hair follicles; on microscopical examination there appears to be an increase of connective tissue reverted to an embryonic type; the fibrils are disassociated and separated by a substance which is said to be mucin; the fibres and fibrils of the connective tissue are gelatinous and swollen; the interstitial lymphatic spaces are enlarged; the cells are hypertrophied; the nuclei enlarged; in fact, a return of the

tissue to an embryonic state. Virchow considers that it is not a regressive but an irritative process, analogous to phlegmasia dolens or elephantiasis, justifying Charcot's nomenclature of "pachydermie." The subcutaneous layer of fat is often very thick. The cutaneous vessels participate in the general condition, the walls are thickened, their lumen reduced, progressing to obliteration.

Kopp, a pupil of Langhans, found thickening of the walls of the vessels in the nerve trunks, and also in the peripheral nerves, the lymph spaces were enlarged, containing edematous vesicles and fusiform cells. Schultz and Renant claim that these findings are not pathognomic as they are found in the normal cases as well as in various diseases.

In the central nervous system Hamilton and Roggowitch describe alterations in the brain; Custue in the horns of the spinal cord; Hadden in the sympathetic. De Quervain, who examined the nervous system of thyroidectomized monkeys, dogs and cats, came to the conclusion that these lesions are not constant, and that there is no pathognomic lesion of the central nervous system in myxedema.

Mendil, Lickenstein, Schotten and Kraeplin have examined the blood and have found a diminished amount of hemoglobin (65 to 68 per cent), the diameter of the red corpuscles seemed to be increased ( $8\mu$  to  $10\mu$ ), nucleated reds were found and in some cases a slight leucocytosis. The coagulability of the blood was reduced. The blood is poor in proteids and inorganic salts.

In cretinism and in cases of infantilism Hofmeister found an arrest of development of the skeleton; exact experiments made on animals showed that the long bones, the vertebral column and the pelvis were one-third less than in the control animals, the head alone developing normally. The epiphyseal nucleus remains cartilaginous, failing to ossify, explaining the rachitic appearance.

In advanced cases of myxedema there is often hypertrophy of the left heart, while chronic nephritis may develop and true edema appear.

*Symptoms.*—When cretinism is fully developed during intrauterine life, which is very rare, it usually results in the death of the fetus, which displays a curious stunted conformation of body with redundant skin, thickened cranial bones, imperfectly formed face and a general irregularity of development. Those who are unfortunately born alive present a remarkable picture of mental and physical deformity, being dwarfed monstrosities with vegetative intellects. The fontanelles are larger than normal, the hair thick and descending towards the eyebrows, so that the forehead appears small, the eyes are dull and expressionless, being usually half closed; the lids heavy and swollen, with only a few eyelashes; the skin is livid during the first month, later becoming a dingy yellow; the nose is flat, the mouth large, the tongue dry and protruding from the mouth, the lips thickened and purple, the lower one being pendulous, over which the saliva flows continuously. The cries are harsh and unnatural; they take the breast sluggishly but never refuse it, appearing to be never satisfied. Should they survive they develop into the lowest form of cretinism.

As a rule however, in both sporadic and endemic forms there are usually no symptoms apparent at the birth of the child, nor do they appear till the sixth or seventh month, the thyroid secretion being probably supplied from the mother through the milk. About the time of weaning it is observed that the child appears dull and that there is a want of proportion in the growth of the limbs and trunk, the head being proportionately much larger than the rest of the members. As the child ages these symptoms become much more marked, the extremities becoming short and stumpy, the subcutaneous tissue thick and baggy and

a goitre may develop with great rapidity. The facies are characteristic, the head is out of proportion to the body, with frontal insufficiency and occipital flattening; the fontanelles remain open until the eighth or ninth year, and sometimes into adult life; the forehead is low, the base of the nose broad, the eyes wide apart and expressionless and half closed, with thickened lid and scanty eyebrows; the lips are thick and purple, the lower lip pendulous with



FIG. 44.



FIG. 45.

A case of sporadic cretinism before and after thyroid feeding.  
(v. Bruns.)

the saliva running over it; the tongue swollen and protruding, the cheeks baggy, of a dirty icteroid hue, without the red patch of health. The teeth are sometimes absent or the first dentition appears late, decaying and falling out early. There may be no second dentition or it may be late in appearing, the teeth being irregular and poorly developed, decaying and falling out early; the lower jaw may either protrude or retreat, but is rarely normal; there is tumefaction of the nasal mucous membrane causing mouth breathing; the ears are thickened and

either waxy or purple in appearance. Fatty tumors are common in the older children, but wanting in infants; they appear in the supraclavicular region behind the sternocleidomastoid muscle in the axilla, between the scapulæ, and in other parts of the body, being often symmetrical and attaining at times the size of a hen's egg. The neck is short and thick, often with a depression above the suprasternal notch. In the endemic form goitre is present in 75 per cent of the cases and is nearly always due to postnatal infection; very rarely are infants born with a goitre. The spine is crooked, having a posterior curvature in the cervical region, probably owing to weakness of the muscles and a compensating anterior curvature in the lower dorsal and lumbar region, causing the abdomen to protrude; there is also a lateral curvature developed. A pseudoumbilical hernia is generally present but contains no gut; true inguinal hernia is not uncommon. The genitalia are usually small and poorly developed, often with various deformities, the testicles do not descend until late and sometimes not at all; the head of the clitoris is enlarged, looking like a penis between the edematous labia majora.

The arms are thick, short and puffy, the fingers are thickened, the legs are cylindrical, giving the impression of props, or they may be bent, resembling rickets; the feet are short and deformed, being too wide for the length, the great toe being swollen. The nails on both hands and feet are brittle and atrophied or may only be rudimentary. The mucous membranes are tumefied, dry and pale, the buccal mucous membrane swollen, as is also the palate and pharynx, the esophagus, stomach, intestines and rectum present a similar appearance, which accounts for the poor digestion, assimilation and severe constipation, with occasional attacks of diarrhea. There is edema of the glottis, the gums are puffy, bleeding easily; the tongue is swollen,



accounting for the thick, peculiar character of the speech. The skin is dry, harsh, scaly and thickened, sometimes over the whole body, with a baggy appearance as if it were too large for its contents; the thickening may be only in patches. At first sight the condition of the skin suggests edema, but as on pressure it does not pit, clears up the diagnosis; there is little or no perspiration and the seba-



FIG. 46.



FIG. 47.

A case of sporadic cretinism aged 6 years before and after thyroid feeding, in the author's practice.

aceous glands fail to secrete, the skin is free from down, the pubes and axillæ may be hairless or the covering sparse, not appearing till very late; the beard is usually absent as are also the eyebrows and eyelashes; the hair of the head is coarse, harsh and scant, receding from the temples, or the middle line, the scalp is more or less bald;

there may be bald patches in various parts of the head; sometimes the hair is very abundant.

The physical development is arrested, cretins of 15 years of age may be no more than two feet six or three feet high; the lips, nose, ears, hands and feet are cold, the temperature is subnormal, and they are very susceptible to cold. The respiration is slow. The digestion is very indifferent, the food being only partially digested, the feces containing undigested proteid, starch and fats; the appetite is usually moderate, but there is a repugnance to meat, which is fortunate, as it is not well borne. It will be remembered that in a previous chapter the feeding experiments on thyroidectomized animals showed that proteid diet increased the symptoms. Mentally their development is very varied; in the lowest types voluntary movement does not exist nor is there any mentality, the faculties being purely vegetative, "*l'homme plante*." Others again are vegetative and reproductive, "*l'homme animal*." Their eyesight is generally fair, but their hearing is often defective. Nièpee found the auditory foramen contracted and the ossicles large and spongy. The intellectual faculties are very limited, as a rule, though by training some few can be taught to take some care of themselves and to articulate a few words which they accompany with exaggerated and ungainly gestures. They are dull, stupid and indifferent to their surroundings; some are passionate and excitable, being guided in their emotions rather by instinct than by reason; they are capable of a certain amount of training and though their affections are not deep they form attachments to those who minister to their wants. Puberty is delayed and may never occur at all. Broca states that in true cretinism it never occurs. Masturbation is the exception, most of them having no sexual desire; a few have paroxysms of great sexual excitement. The disease progresses slowly

with no tendency to improvement; they are not, however, very susceptible to the diseases of childhood, but usually succumb to some pulmonary trouble before 20 years of



FIG. 48. —Cretin, aged 12 years, with the permission of Dr. A. C. Roger, Fairbault, Minn.

age, a few live till 40 or even longer. Rachitis is a common complication; in fact, it is said that all cretins are rachitic, but this is highly improbable, the nondevelopment and ossification of the epiphyseal nuclei being mis-

taken for rachitis which it closely resembles. Asthma is a common complication, possibly due in a certain number of cases to persistent thymus.

The blood is low in hemoglobin and in red blood corpuscles, while the arterial blood is of a venous hue from its containing a reduced quantity of oxygen.

The most marked symptom is the shortness of stature, in illustration of which Hertoghe, of Antwerp, quotes a case which had not grown since his twelfth year, who at 27 was four feet six inches high and weighed 81 pounds, and who grew one inch in three months on thyroid treatment, and another who had not grown since his fourteenth year and at 18 was five feet one inch, weighing 110 pounds. In these cases the arrest of growth had commenced about puberty, the patient ceasing to increase in height but gaining in weight.

#### CRETINISM IN ANIMALS.

Cretinism in animals has occasionally been recorded. Eberth in 1878 described a monster calf which he considered a cretin. Gurlt in 1877 describes a few cases. In South Kensington Museum there is a stuffed specimen and the Royal College of Surgeons possesses the skeleton of a typical cretin calf.

Cretinism appears to occur with curious frequency in Dexter-Kerry cattle, a breed which has become popular in England in recent years. C. G. Selegmann in the *Journal of Pathology and Bacteriology* for March, 1904, describes the occurrence of cretins in the herds of this particular breed. They are usually born prematurely, with short-rounded head, depressed nostrils and projecting mandible, combined with extreme shortness of the limbs. They have been christened "bull dog calves" by the herdsmen. They seem to occur with considerable frequency in all herds of this breed irrespective of locality. In 1891 one herd produced

seven cretins out of twenty births, or 35 per cent, another herd produced twenty-seven calves, five of which were cretins or 18.5 per cent. The pregnancies of the cows are abnormal; the calf is usually dropped about the sixth, seventh or eighth month, the cow's belly begins to swell, becoming enormously distended, before the cretin is born;



FIG. 49.—Skull of Cretin calf. (C. G. Selegmann.)

the cow loses a large quantity of water, decreasing in size before labor. When this occurs months or weeks before labor, a further abnormal increase followed by a decrease may occur. After the birth the lochia is more abundant. The placenta, instead of coming away in from one half to four hours after delivery as normally, is got rid of slowly and in fragments, the process often lasting two or

three days. The thyroids of the cretin calves examined were represented by a couple of more or less rounded edematous dark purple colored masses one on each side of the trachea, the isthmus being absent. On microscopical examination the cells appear to be only partially or not at all arranged in vesicles, usually forming irregular masses or branching columns with or more frequently without a lumen. Colloid is commonly absent, occasionally present in a few vesicles only. Injection of the gland substance into cats did not produce the typical fall in blood pressure. These observations of Selegmann are of great interest and further investigation may show that sporadic cretinism may be due to placental disease.

## CHAPTER XI.

### MYXEDEMATOUS INFANTILISM.

Myxedematous infantilism has been defined as an anomaly of development characterized by the persistence after puberty of the morphological characters of childhood, the arrest of the physical development being often accompanied by a general mental deficiency corresponding to the physical retardation.

In 1871 Faneau published an article on femininism and infantilism in the tuberculous. Joffroy, Bourneville, Sollier, Souques, Barety, Féré, Marfans, Guinon, Capitan, Richer, Gerard and others published reports of interesting cases of femininism, infantilism and senilism, but these forms were not recognized in medical literature till the last decade, when Brissaud and Hertoghe, of Antwerp, described the etiology, symptoms and treatment. In 1894 Brissaud, in his lectures on myxedema and cretinism, at the Salpêtrière described a less severe form of cretinism, consisting of a partial arrest of physical and mental development, at the same time showing to his class a boy of 18 suffering from thyroid insufficiency, who presented all the symptoms of infantilism. Miede in 1895 described the condition of the genital organs in these cases and drew attention to their arrested development, pointed out that many of the cases whose want of development was attributed to congenital syphilis, or to tuberculosis were really suffering from hypothyroidea, drawing attention also to the possible connection of giantism, dwarfism, rachitis and obesity with an abnormal functionation of the thyroid gland. Hertoghe published his observations in the same field, assuring that there was no infantilism without insuf-

iciency of the thyroid gland. Hofmeister, Gley, Broca, Brissaud and others followed, showing in the most conclusive manner the important part played by the thyroid gland in physical and mental development.

The etiology of infantilism, to be more definite, myxedematous infantilism, is undoubtedly a lesion of the thyroid gland which has resulted in a deficient secretion. The cause of this lesion may be, though probably very rarely, the result of partial sclerosis of the gland from hereditary syphilis or tuberculosis, but in the vast majority of cases it will be found on obtaining the history of the case that the patient has suffered from some acute disease in childhood which has affected the gland, producing a so considerable sclerosis that it is incapacitated from secreting sufficient for the needs of the organisms.

The symptoms of infantilism are those of cretinism in an attenuated form, varying with the age at which the disease commenced, and the amount of the destruction of tissue in the thyroid gland. The following symptoms may appear but will never or rarely all be found in a single case. When the physician is consulted upon the nondevelopment of a patient, if he finds a few of these symptoms, especially if coupled with the history of an acute disease antedating the commencement of the arrest of development, he is justified in prescribing thyroid feeding.

The patient appears old for his years, short in stature but usually of symmetrical proportions, though stout and heavy. The face is large, round and moonlike, with a stupid surly expression, pale and waxy looking, the scalp and the skin of the face are thickened, the eyes somewhat wide apart, the mouth large, the nose broad, the hair is usually abundant but coarse up to about the twentieth year, when baldness commences, the mucous membranes are turgid, especially in the nasal passages and larynx,



causing mouth breathing with a peculiar harsh nasal intonation as if the patient were suffering from a severe cold;



FIG. 50. —Before treatment.  
(Hertoghe.)

FIG. 51. —After 6 months' treatment.  
(Hertoghe.)

the tongue may be swollen, which has a characteristic effect upon the articulation. The neck is short and thick,

the body usually well nourished, but there is a thickening of the skin which disguises the outlines of the muscles and



FIG. 52.—After 1 year's treatment.  
(Hertoghe.)

FIG. 53.— After 2 years' treatment.  
(Hertoghe.)

bones. The hands are thick and of a bluish tinge, the veins being distended. The feet are flat, short and broad.

The hands and feet are cold, suffering from chilblains in winter and fetid perspiration in summer. The skin is dry and harsh, perspiration being absent or subnormal. The organs of generation remain infantile, at 23 there may be no more sexual development than in a normal child of 10. In females menstruation is delayed and even when established is scant, irregular and painful. The nondevelopment of the sexual organs is one of the most constant and important symptoms from the diagnostic standpoint, though occasionally the organs may be normal. The teeth



FIG. 54.—Skiagram of the hand of a type Loraine, 17 years old.

are small, irregular and decay early. If the disease commences in early childhood, the abdomen may protrude and there may be a slight pseudo-umbilical hernia. The limbs are often round and straight, having the appearance of columns. There is a persistence of the epiphyseal cartilages which can be distinctly seen with the X-rays.

The mentality is sometimes apparently not impaired, the child being equal to the average; in other cases he is

mentally dull and can only be taught to read and write with difficulty. This difference between the physical and mental development has caused some observers to come to the conclusion that on the thyroid gland depends the physical growth while the mental development is associated with the parathyroids.

There is, however, a want of mental development in the childishness of the patients; although their education may be up to the average there is an arrest of development in

ideas and mode of thought; they are childlike in manners, easily provoked to tears or laughter, associating with those much younger in years and continuing to take interest in the amusements of children; often there is a certain amount of effeminacy which suggests sexual perversion.



FIG. 55.—Skiagram of the hand of a normal child, 6 years old.



FIG. 56.—Skiagram of the hand of a case of myxedema, 19 years old.

The pulse and temperature are usually normal, but the respiration is often labored and noisy, due to adenoids or to hypertrophy of the mucous membranes of the air passages.

Albuminuria and rachitis are two diseases which may exist with thyroid insufficiency, the former may disappear under treatment. There is also a hyperazoturia occurring at intervals, owing to a retention of nitrogen.

In weighing the symptoms in these cases the age at which the disease developed has to be taken into consideration, the older the child at the commencement of the disease the more obscure and atypical will be the symptoms.

Infantilism of the type Loraine has been described by

Brissaud, Loraine, Faneau de la Cour and others as a particular form of arrested development, differing from myxedematous infantilism in many points, and appears to be due to a congenital nondevelopment of the arteries, sometimes combined with thyroid insufficiency. Admit-



FIG. 57.—Skiagram of the hand of a type Loraine, 16 years old.

ting that there is such a condition as congenital nondevelopment of the arteries, in which the aorta, the renal and pulmonary arteries, etc., are reduced in size, it is evident that with the other organs the thyroid will not receive sufficient nourishment and will consequently be arrested in its growth and functionation. Much has been written for and against the existence of a condition of congenital narrowing or arrest of development of the aorta and blood vessels, but there seems

to be no reason why such a condition should not exist in the blood vessels as in other organs of the body. Suter, in the "Archives of Exp. Path. and Pharm.," vol. xxxix, holds that there is no such thing as congenital narrowing of the aorta but that the variation in calibre found at autopsy is merely a question of greater or less elasticity; in any case, it appears that some aortas are at least more elastic than others. Ohlmacher, in his researches on congenital epilepsy, found narrowing of the aorta in nearly every case. That aortic narrowing must have far-reaching pathological effects, from the insufficient blood supply to the various organs and upon the heart from the extra work thrown upon it, is evident. A congenital mitral stenosis would act in much the same manner.



In the form of infantilism under discussion there is an hypertrophy of the left ventricle with a high blood pressure and small arteries, the pulsation of the aorta cannot be felt in the neck, the temperature is subnormal; the physical appearance is not that of myxedematous infantilism. The patient is short of stature, at the first glance looking like a boy, but on closer observation he appears as a small adult, which has been well described as a man seen through the large end of an opera glass; the shoulders are large, the chest narrow, the bony projections well marked, the muscles without being strongly developed are distinct, having lost the fatty covering of childhood. He is a man in miniature giving the impression of effeminacy and debility.



FIG. 58.—Skiagram of a normal hand, 20 years old.

He may have little or no hair on the face, pubes or in the axillæ, the sexual organs are small but developed in proportion to his size. The head, which in the myxedematous form is usually large, is small, the face is often pitted with psoriasis, the feet small and flat, the teeth decayed, the gums red, irritable and lined with tartar. The fontanelles close early and the epiphyses ossify normally, differing in this from the myxedematous form. Fetid perspiration of the feet is common. Nocturnal incontinence of urine is associated with this form of infantilism.

It is by no means evident that this form of infantilism is directly due to hyposecretion of the thyroid gland; on the contrary, it is evident that the arrested development

of the circulatory system plays an important part; other glands are probably trophic in their function, the testicles

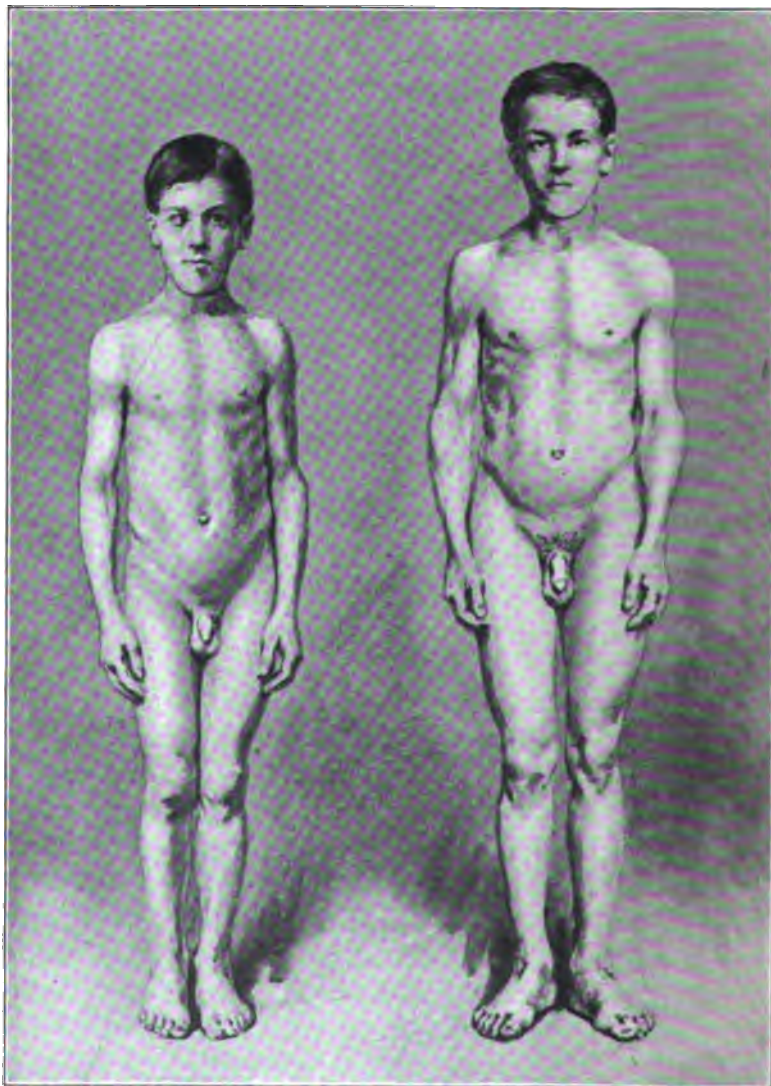


FIG. 59.

FIG. 60.

Infantilism aged 19 yrs.

Before treatment.

Height, 4' 6¼"; weight, 76 lbs.

After 1 year's treatment.

Height, 4' 11½"; weight, 92 lbs.

and ovaries, the thymus, the suprarenals and the spleen may all have a function to perform necessary for the complete and normal development of the organism which has not as yet been discovered. Many of these cases, however, improve on thyroid treatment, though not so completely as in the case of myxedematous infantilism.

If a skiagraph of the hand or long bones is taken and it is found that the epiphyses are ossified it is evident that increase in height will not follow any treatment, but should the intraosseous cartilage still persist the probabilities are that thyroid treatment will stimulate growth.

Anangioplasia, or the congenital diminution of the lumen of the larger arteries, is considered as a separate form of infantilism by some authors, and has been found associated with the lymphatic constitution in many cases of so-called idiopathic epilepsy by Ohlmacher. Such a condition will produce an arrest of development of the organism as a whole, acting upon the various organs of the body, reducing their growth and secreting powers. There are three quantitative conditions of the circulation required for the nutrition, growth and functionation of an organ; that is to say, the minimum amount of blood will nourish the organ and prevent degeneration from starvation, a further quantity is required for growth and a still further quantity for functionation, consequently any interference in the quantity of the blood supply will first cause loss of function, a further diminution will arrest growth and development, and a still further decrease will cause starvation and death. Further, the total quantity of blood in circulation will be materially decreased by the narrowing of the arteries.

Other organs besides the thyroid may be implicated in causing infantilism. Imperfect action of almost any organ of the body can be conceived as arresting development, either physical or mental; it has been described as



occurring in disease of the abdominal organs, as the liver and pancreas, and especially in that condition of lymphatic hypertrophy known as status lymphaticus, in which the lymphatic tissues all over the body are enlarged, especially the mesenteric and intestinal glands, a persistent thymus

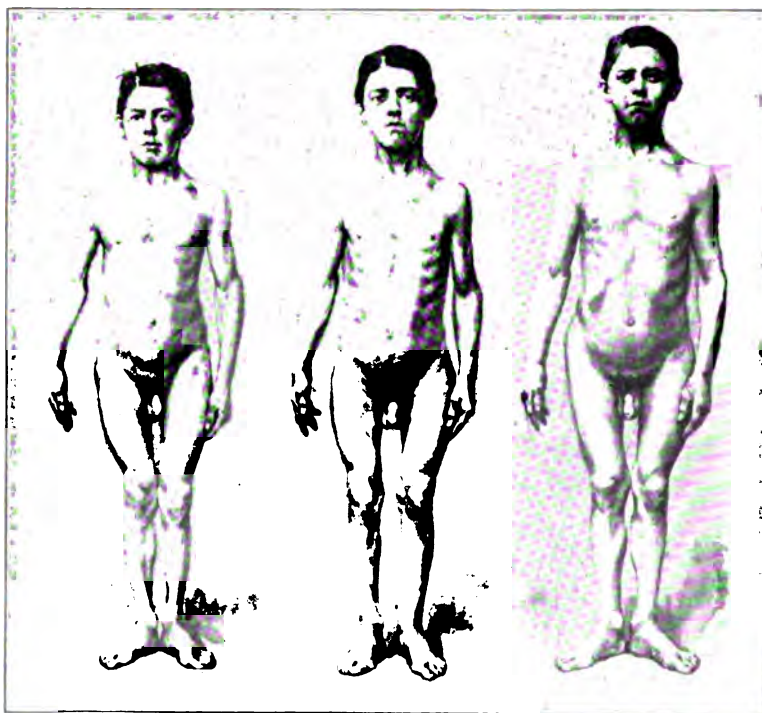


FIG. 61. FIG. 62. FIG. 63.  
Before treatment. After 4 months' treatment. After 7 months' treatment.  
Infantilism simulating type Loraine, aged 21 years. (Hertoghe.)

being also generally present. Cardiac lesions, such as mitral stenosis, or insufficiency, will also probably produce a defective development in the same manner as congenital narrowing of the vessels produces a condition which, though simulating, is not identical with infantilism. There is no doubt the testicles and ovaries have an effect

upon development, both physical and mental, and certain cases of infantilism of the type Loraine are said to have been improved by the administration of orchitic extract when it was evident that the testicles were poorly developed.

The close association of the thyroid with the physical and mental development, as shown in cretinism and myxedema, point to its being a probable primary cause in the majority of cases, the lesions of the heart, liver, pancreas, etc., being secondary to the general want of nutrition.

Dr. Platauf has described a disease under the name of ateleiosis (*ατελείωσις*, not arriving at perfection), of which a few cases are on record. Dr. Hastings Gifford has described some half dozen cases as follows: The most characteristic features of this disease are (1) its abrupt onset; (2) the absence of perceptible cause; (3) the presence of infantilism of a conspicuous kind; (4) the retention of unimpaired intelligence, and (5) a special tendency to marked delay of development of the sexual system. He states the disease may appear at any of the developing periods of life and divides them into groups according to the age at which they develop. Group I, fetal origin; Group II, early childhood; Group III, that period which intervenes between childhood and maturity, each presenting special aspects depending on the development at the time of the onset of the disease.

*Group I.*—Fetal ateleioses is accompanied by certain of the characteristics of microcephaly. There may be no abnormal smallness of the brain when compared with the size of the body; in fact, the brain may be disproportionately large. It, therefore, seems as though the characters of microcephaly were due to the fact that a virtual arrest of the brain growth takes place at a time when the brain is so small and so undeveloped as to be incapable of performing its proper functions. In only one of Dr. Gif-

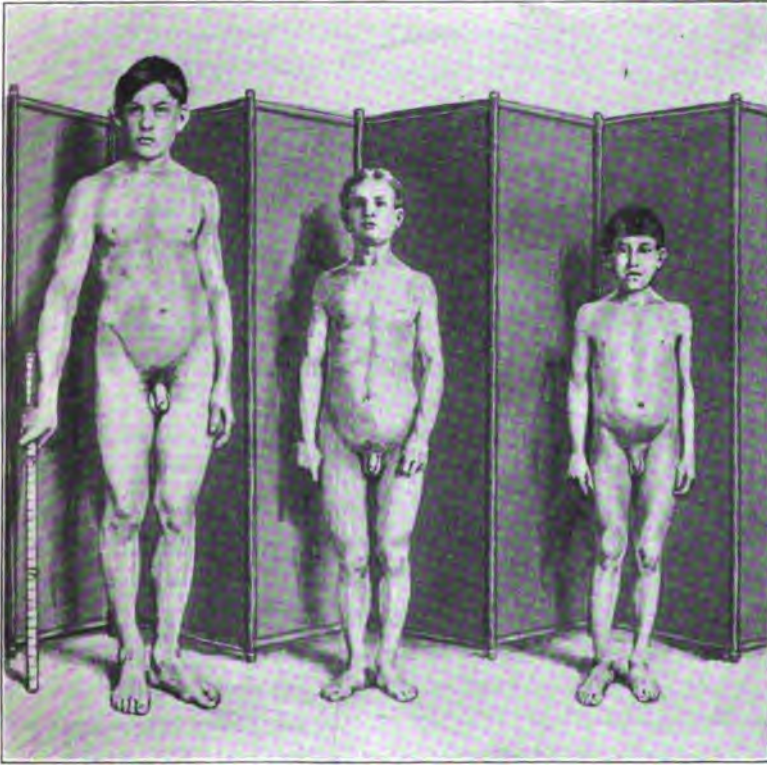
ford's cases was there imbecility together with the physiognomy which is characteristic of ateleiosis.

*Group II.*—The disease is most characteristic when it commences in early childhood. It may occur in more than one member of the same family and in one of his cases the father was a dwarf who had been exhibited. The disease resembles cretinism in the almost complete arrest of growth and development. The form of the body remains for the rest of life with those infantile characters which it possessed at the time of the onset of the disease. The stature is preternaturally short, while the head is large when compared with the adult, the face is broad and flat, the nose sunken at the bridge, while the head is high when measured from the ear to the vertex. The childlike form and physiognomy, added to a look of independence combined with the wrinkling and weltering of the skin, give an appearance which is not that of a child or of a cretin (?), and is still less like that of an ordinary adult.

In describing a case Dr. Gifford says the patient was 28 years old at the time of the description. He had ceased to grow normally at 18 months and by measurement he continued to grow till his twenty-seventh year. He left school at 16, after passing the sixth standard. "His general configuration is that of a child, the outlines of the muscles are hidden by fat while the contour of both body and limbs is rounded and childish in appearance. He is 3 feet  $7\frac{1}{8}$  inches tall, and his head  $19\frac{1}{2}$  inches in circumference, and weighs 57 pounds. His head is large, his limbs short, and the relative lengths of the segments of the limbs more nearly resemble those of a child than of an adult. His height is equal to that of an average child between 6 and 7. By means of the radiograph the bones of the hand and wrist were examined, showing ossification equal to that of an average boy of 13. On the other hand, his sexual organs are no more developed than are those of

an infant. It will be seen that the rate of development of different parts is by no means uniform."

A second case is described by Dr. Gifford, as follows: "He has the broad, flat face and retroussé nose of childhood, but combined with it is the harsh and wrinkled skin



|                                 |                                   |   |
|---------------------------------|-----------------------------------|---|
| FIG. 64.                        | FIG. 65.                          | FIG. 66.                                      |
| Normal boy, 17 years<br>of age. | Type Loraine, 27<br>years of age. | Myxedematous Infantilism,<br>18 years of age. |

of middle age. The countenance is of the cretinoid type, but it differs from that of cretinism in that the lips are not thick and that the whole face is lighted up by a look of intelligence. Sexual hair is completely absent from the face as from every other part, but the hair of the head is

fairly abundant and encroaches upon the forehead in a way which is more often seen in children than in adults. His muscular strength is equal to that of a child of his height. All the organs of secretion and special sense appear to be normal. He sweats on exertion and is not particularly sensitive to cold. His voice is more treble than that of an adult. The thyroid gland can be detected. Dentition is backward, the permanent canines having apparently not long protruded through the gums, while the temporary canines of the left side have not been shed. His general health is excellent, and he shows no signs of syphilis, rickets or of any other disease." His age is not stated.

Dr. Gifford does not state the treatment, if any, nor the result, but it seems as if the majority of the symptoms described in both cases were those of myxedema, possibly associated with a pathological condition of some other organ which modified the disease, making it atypic.

*Group III.*—Ateleiosis of this group beginning in adult life is not so typical in physical features as the first two groups. In these cases there is a curious combination of the size and facial characters of a boy combined with the mannerisms of an adult. The skin, however, has not the soft, delicate tinge of youth, but is more like that of the aged or weather-beaten face of grown-up people. In ateleiosis there is at times a normal development of the sexual organs with powers of reproduction and the bones may ossify normally at puberty.

The description of this group is meagre, but shows little or no evidence of myxedema, and applies more to those who have remained childish from the want of proper environment.

Senilism is another form of disease often commencing in early childhood, which may be mentioned here as it may possibly be due to a hypersecretion of the thyroid.

Normal senilism may occur at various ages, some be-

coming senile at 55 or 60, others again being vigorous in both mind and body at 80 or more. This normal senilism is due to the changes in the arteries and the chemical activity of the cells.

On the other hand, precocious development is an indication of disease and a sign usually of early decay. Sexual precocity is probably the most common symptom, sometimes combined with rapid growth in height and weight. A well-known case of great premature development is that of Thomas Hall, known as the "fat boy of Willingham." In his case there was a premature development of the sexual organs at the ninth month; at 3 years of age he was 3 feet 9 inches tall and weighed 56 pounds, and his muscular strength was equal to boys of 7 or 8 years. His voice was "changed." His intelligence was above the average for his age, while his sexual organs resembled in size those of a man. At the age of 5 he began to grow a mustache; at six he died of consumption.

In another case the first dentition began at 10 months, the child could walk at 12 months, and at 13 months he was 3 feet high and weighed 57 pounds, the head being 20 $\frac{3}{4}$  inches in circumference. His mentality was about equal to his years, he was weak, not being able to sit up straight without support, and there was an enormous growth of subcutaneous fat; the skin was pale and unhealthy. On close inspection coarse dark bristly hair could be seen sprinkled sparsely over the body and limbs; that on the upper lip and on both sides of the face being longer than elsewhere and resembling in quantity that which grows at puberty in normal boys. His sexual organs were about equal to those of a boy at puberty. He suffered from syncope and died in a sudden attack at the age of 14 months.

Progeria is a form of senilism which simulates ateleiosis, being characterized according to Dr. Gifford by its abrupt

onset, the absence of perceptible cause, the presence of a conspicuous form of senilism, the retention of intelligence. Only two cases appear to have been reported, in one of which a postmortem examination showed atheromatous conditions of the arteries and the valves of the heart, which would account for most of the symptoms.

Yet another form of senilism has been reported by Drs. A. S. and T. B. Charcot, in *La Nouvelle Iconographie de la Salpêtrière*, and named by them "geromorphinicutanée." The patient was a young woman of 20, having the appearance of being 60 years of age owing to the skin hanging in loose folds so that at the neck it hung down like the dewlaps of an ox. In the other cases of progeria reported there was atrophy of the hair, nails and breasts, though in the above case these symptoms were not present.

Achondroplasia is a form of arrested development which may be mistaken at first sight for myxedematous infantilism. It was first described by Parrot and Depaul in France and by Kirchberg and Marchand in Germany, Dr. Porak writing a monograph on the disease in the *Nouvelles arch. d'Obst. et de Gyn.*, 1889-90. In 1892 Kaufmann studied three skeletons of fetal achondroplasia. In 1893 Thomson reported a case, Apert, Hergott and Marie other cases in 1900.

The disease is usually mistaken for rachitis; the most marked traits are the large size of the head and trunk, the shortness of the limbs, the forearm and the leg being longer than the arm and thigh respectively.

The symptoms consist of a macrocephalic condition which may simulate hydrocephalus; the head is round, the frontal and parietal bones projecting, the face large, the features gross, the root of the nose depressed, the nose enlarged and rounded at the end, the nostrils dilated, the roof of the mouth arched. The depression at the juncture of the lumbar vertebræ with the sacrum is very marked,

the latter being elevated, giving the impression of a dislocation. The hands are small and square, reduced in all dimensions, the fingers shriveled and of almost equal di-



FIG. 67.

FIG. 68.

Achondroplasia. (Comby.)

mensions. Sometimes the legs are bowed, at others the knees are inclined inwards. The muscles are usually abnormally developed and they are often athletic dwarfs.



The genitalia are well developed, many of them having families.

The bones which develop directly from the primitive embryonic tissue, as the clavicle, ribs, frontal and parietal bones, etc., which do not pass through the cartilaginous stage, escape the dystrophy, which explains the normal development of the trunk. On the other hand, the ossification of the epiphyseal cartilage is arrested, the bones of the limbs are unable to lengthen. In distinction from rachitis, achondroplasia usually commences from the third to the sixth month of intrauterine life, while rachitis is a postnatal disease. In achondroplasia there is penetration of the periosteum inward, between the epiphysis and the diaphysis, which is not seen in cretinism or rachitis.

## CHAPTER XII.

### MYXEDEMA.

Myxedema in the adult is usually a slowly progressive disease, though cases are on record where it has developed rapidly. Charcot and Ord report cases which commenced with a chill, in one case with hematuria, developing within a week. Byrom Bramwell states that in one of his cases the disease appeared in a few days after an attack of influenza. It is probable that in these cases the disease had been latent, unobserved by the patient for some time, until some intercurrent disease made a call upon the gland for an increase of secretion to which it was unable to respond.

The initial symptom is an intense lassitude and debility. Women who have heretofore been bright and active in their duties have a repugnance to exertion both of body and mind. This is associated with an increase of bulk of the body, a dryness of the skin and an increased susceptibility to cold. I have observed that in the very early stages there is a hyperactivity of the sebaceous glands, the surface of the skin being greasy, while the head is full of dandruff. Frontal headache is often a cause of complaint in the earliest stages. As the disease advances the face, trunk and limbs increase in bulk with the appearance of edema, except that the skin does not pit on pressure nor does it exude fluid on puncture; there is an appearance as if the skin were too large, hanging in thick folds on various parts of the body. Ordinary dropsy of the feet occurs in about 20 per cent of the cases.

At the first glance the observer notices a heavy, stolid expression of sorrowful immobility, the face is full, broad, coarse and round, looking puffy and swollen; in some cases

the wrinkles are flattened out; the upper eyelids droop over the eyeballs, causing a consequent elevation of the eyebrows, producing transverse wrinkles in the forehead as in paralytic ptosis. Sometimes the lids are so swollen that they completely cover the eyeball and the patient has to raise them with the finger in order to see at all. The skin of the eyelid has a peculiar translucent appearance.



FIG. 69.—Myxedema.

Baggy swellings appear under the eyes, which suggest Bright's disease. The cheeks are pendulous and puffy. The thickening of the skin usually commences in the scalp anterior to the ears and in the nasolabial folds. Owing to the capillary dilatation there is often a rosy tinge over the malar bone, abruptly limited by the lower margin of the orbit, contrasting strongly with the dingy yellow color of

the rest of the face. The lips are thickened, especially the lower, of a purplish color, feeling firm and tense to the touch. The tongue is swollen, the gums edematous, bleeding easily, the buccal mucous membrane is also edematous, sometimes to such an extent as to be injured during mastication. The tonsils are enlarged, the uvula, pharynx and larynx are edematous. The swelling of the soft parts of the back of the mouth may be so considerable that the patient may experience difficulty in swallowing, complaining of a choking sensation. The nose is broad and coarse looking, the mucous membranes of the retronasal cavities are swollen, impeding respiration, which becomes aggravated with the least cold. The patient usually complains of easily catching cold, of a frontal headache and of a "stopped up" feeling, such as is associated with acute coryza.

The neck is usually broad and thick, with puffy elastic swellings above the clavicles. Though the neck appears thick the rings of the trachea can be distinctly felt and yet the thyroid may not be palpable. It is, however, very difficult to palpate the thyroid gland during life even in the healthy subject, and it can be assumed that if it can be so detected it has increased in size.

The hands are enlarged, thickened and spadelike, the fingers broad, thickened and flat, the patient complains that they feel numb and that they are unable to perform the finer movements, such as sewing or buttoning the clothes; in some cases the swelling is so great that they are unable to close the hands; the feet present the same changes and, as before stated, there may be true edema of the feet and ankles. The abdomen is full and large, the trunk as a whole being increased in size; the vulva and external genitals may be swollen.

The skin is coarse, harsh, rough, dry and scaly looking, it may be split up into lozenge-shaped areas, wrinkled and

cracked, resembling ichthyosis. The sudoriferous and sebaceous glands cease to secrete, the absence of sweating, even in hot weather or after muscular exertion, is a very characteristic symptom. The electrical resistance of the skin is much increased owing to its dry condition. Byrom Bramwell notes the presence of flat moles and warts. On the abdomen appear patches of yellow discoloration resembling the so-called liver spots; there is often a very marked desquamation, so much so that the scurf can be scraped from the bed linen in quantity. The hair of the scalp has a tendency to fall out, complete baldness occasionally occurring with great rapidity, the eyelashes and eyebrows become thin and may fall out entirely. There is an incrustation on the scalp, eyebrows and eyelids. The fine hairs at the back of the neck fall out and give a peculiar bare appearance. The hair becomes coarse and brittle and may change color. In the axillæ and the pubes the hair falls out, the parts may become quite bare.

The nails are brittle, dry and opaque, the teeth carious and loose; in many cases there is an increased secretion of saliva which may be very troublesome. It has been observed that the secretion from the parotid gland in these cases contains an excess of mucus. There is also a running from the eyes and nose.

The mucous membranes of the stomach, intestines and rectum share in the general tumefaction of the mucous membranes, producing malnutrition and the obstinate constipation from which the patients invariably suffer. The stomach examination after the Salzer-Ewald testmeal shows a marked hypochlorhydria, sometimes anachlorhydria, usually with excess of organic acid, also excess of mucus, want of motility and of absorption.

There is a wheezing inspiration in advanced cases which is often ascribed to asthma, the patient may make a noisy

gasping inspiration after a sentence. From the edematous condition of the nasal mucous membrane the patients are compelled to breathe through the mouth, consequently their intonation is harsh, rasping and nasal; when adenoid growths are present, which is often the case, the breathing is noisy even at rest. Owing to the thickening of the vocal cords and the enlargement of the tongue the speech has a peculiar sound as if the patient had something in her mouth. Owing to the impaired mentality the speech is slow and deliberate.

The mental condition is always abnormal, resembling dementia; there is a lack of quickness of perception, a slowness of thought, an emotional depression and suppression combined with listlessness and torpor; the repugnance to exertion of any kind is a marked feature and is often the first symptom noticed by the patient. Hallucinations of sight and hearing are not uncommon; there may be a singing in the ears and even "hearing voices." The hallucinations of sight resemble those of alcoholism; less often hallucinations of taste and smell occur, any of which may be so severe as to prevent the patient from sleeping; as a rule, however, patients sleep well or excessively. Some few are garrulous, continuing to talk regardless of questions or interruptions, simulating mania. Usually these patients are even tempered, but sometimes very irritable, having violent fits of passion; others are suspicious of their friends and of themselves. The memory is much impaired. The placidity and stolidity of myxedema is in marked contrast to the excitability and perpetual unrest of Basedow's disease. The mental symptoms may become so severe as to be insanity, rarely maniacal. They are usually melancholic.

The tactile sensibility of the skin is delayed or diminished, sight and hearing impaired. Headache, cramps, neuralgic pains, faintness, giddiness, tinnitus aurium and muscular pains are often accompanying symptoms.

The gait is heavy and clumsy, the muscular power is much impaired and there is a certain amount of loss of coördination, the patient being apt to stagger and even to fall. The walk, owing to the increased size of the body and the muscular weakness, combined with the slowness and numbness of the movements, has been termed the "hippopotamus gait."

The reflexes are usually diminished, the knee jerks often abolished. The sensibility is often especially impaired in regard to heat and cold, the patients being extremely susceptible to variations in external temperature, complaining of feeling cold. It has been observed by Horsley and others that thyroidectomized animals would survive the operation much longer and symptoms even not developed at all as long as the subject was kept in a room at a high temperature. The patients often complain of a tingling or pricking sensation of the skin. The body temperature is subnormal, being 96.5 degrees F. or even a little lower. The subnormal temperature and the susceptibility to cold are due to decreased oxidation and a pathologic condition of the cutaneous capillary system.

The pulse is slower than normal, soft and weak, the heart's action feeble, the second sound accentuated, the mean blood pressure increased, the heart dilated, the cardiac muscle degenerated and the arteries atheromatous; in the latter case thyroid feeding must be conducted with caution. Fainting may occur, palpitation is often complained of after exertion. Anemia is usually present, the hemoglobin may be as low as 60 per cent and the red corpuscles reduced to 3,000,000.

The appetite is poor, as is the digestion; obstinate constipation is the rule, diarrhea the exception, but as is common in hypochlorhydria, there are often severe attacks of diarrhea without apparent cause.

In females amenorrhea is the rule, menorrhagia the ex-

ception. In cases of amenorrhea there may be occasional profuse hemorrhages; there is also a marked tendency to hemorrhage owing to the high mean pressure and disease of the vessels as well as to the reduced coagulability of the blood. Epistaxis and bleeding from the gums are common, any small injury may bleed profusely. Should a case become pregnant, which rarely happens, postpartem hemorrhage should be guarded against.

The urine is usually normal or increased in quantity, the specific gravity low, total nitrogen low, urea nitrogen decreased, ammonia nitrogen increased, uric acid nitrogen decreased or normal, and the residual nitrogen increased. The carbon nitrogen factor is high, the carbon elimination being greater than the nitrogen; oxalic acid is often increased, total sulphates are low, ethereal sulphates high and the neutral sulphur very high. Indican is excessive, bile pigment and indoxylglycuronic acid are often present, the latter sometimes in sufficient quantity to reduce Fehling's solution. Albumin is sometimes present, and albumose. Byrom Bramwell reports a case where serum globulin was present but no serum albumin. It would have been interesting in this case to have had an analysis of the blood, in order to have observed the proportion of serum albumin and serum globulin. I have found nuclealbumin in several cases, but rarely serum globulin or serum albumin, except in cases where there was evidently an associated kidney lesion.

#### INCOMPLETE MYXEDEMA IN THE ADULT.

Between the healthy condition of the gland and its complete or almost complete cessation of function there are necessarily an infinite number of degrees producing varying symptoms, more or less acute, giving varied clinical pictures, which it is of importance to recognize as pointing to possible relief by thyroid feeding. In the cases where



there is a hypothyroidea, either congenital or acquired, a condition of premature senility is produced, the patient appears old for her years, she becomes gray early, either generally or in patches, the hair may fall out rapidly either over the temples in front, along the median line or at the back of the head, the down on the back of the neck disappears and there is a baldness extending up to the occipital protuberance, where it looks scanty and ragged, the skin is yellow, shriveled and coarse, the hair feels brittle and dry and is fluffy, looking untidy; there is an incrustation of the scalp or there may be a large quantity of dandruff, sometimes there are bald patches. These changes are often concealed by the barber's art and must be especially looked for. The eyebrows and eyelashes are thin or may be entirely absent; there is a scaly condition of the skin at the external angles of the eyebrows, often accompanied with itching. The teeth are generally decayed, especially the molars; the gums are inflamed and soft, bleeding easily; the teeth are covered with black or green tartar, rarely yellow, especially the incisors of the lower jaw. The tongue is swollen and indented with the teeth. The nasal accumulation of tartar forces back the gums, the teeth become loose and fall out. The tonsils are swollen, often hypertrophied. The mucous membrane of the pharynx is red and edematous, adenoids are often present. The fossæ are contracted, being obstructed by the swollen mucous membrane; adenoids are common; sometimes in mild cases the nasal fossæ are normal except during menstruation or a slight cold, when the posterior portions become engorged; the nasal condition causes the patient a great deal of inconvenience, and is generally attributed to a chronic catarrh to which the patient ascribes her mental heaviness and drowsiness. Sometimes the condition produces continued sneezing. The voice is high pitched and leathery, usually being more discordant during menstruation and pregnancy.

The headaches which are often attributed to cerebral anemia are of two kinds, sometimes appearing in the frontal sinus or behind the orbits, as in acute coryza, or they may appear in the occipital region. They are often described as migraine, but they differ from true migraine in being at their worst in the morning, disappearing as the day wears on or after a full meal. The patient is so accustomed to this that she may not complain of it till her attention is called to it; she usually attributes the falling out of the hair or its turning gray to these headaches, or again she may account for the headaches by the condition of her teeth. The thickening of the skin, which is so marked a symptom in complete myxedema, is not present, or only very slightly; there may be a puffiness under the eyes, a red patch on the cheek extending to the nose; the skin has a dirty yellow color or it may have a clear waxy appearance; the raised eyebrows and transverse wrinkles of the brow may also be present; the whole expression is one of sorrowful fatigue. Murray, in the *Brit. Med. Jour.*, 1898, describes cases which he calls "early thyroidal fibrosis," in which he has observed hallucinations of sight and hearing, the patients seeing objects indistinctly defined resembling cats, mice, rats, etc., which rapidly traverse the room when it is well lighted. Buzzing and ringing in the ears is common and may go so far as to take the distinct sound of bells. Hertoghe has made the same observation.

There is also a rachialgia with pain between the shoulders the patient suffering from insomnia, falling into a sound sleep in the early hours of the morning, but is shortly awakened with pains which she describes as though the back were being wrenched asunder, so intense is the discomfort that sleepy and tired though the patient feels, she is unable to remain in bed and rises tired and unrefreshed, with a headache and rachialgic pains, which, however, become less, disappearing entirely as the day ad-

vances only to appear again on the following morning. Often the joints and muscles are painful, usually attributed to rheumatism, but the temperature is normal or sub-normal and the pains do not yield to rheumatic treatment; as the case advances the pains may appear first in one part and then in another, or in several places at once. The patient often complains of chills, which may occur with great regularity at a given time of the day, usually be-



Fig. 70.—Before treatment.

Fig. 71.—After 6 months' treatment.  
Incomplete Myxedema.

tween 4 and 6 o'clock; they simulate malaria, but the plasmodia are not present nor do they yield to quinin. The patient complains of feeling cold in spite of coverings and wraps, the feet and hands being especially susceptible. A shortness of breath is a very constant symptom, sometimes very slight and only noticeable on muscular exertion or going upstairs; at times it is accentuated. Occasionally, in advanced cases, the patient makes a quick, short noisy inspiration after each sentence, usually ascribed to asthma or embonpoint. This oppression exists even when the patient is not stout, and on careful examination of the

chest dilatation of the base of the thorax will be found. Pulmonary emphysema is often difficult to explain and may be looked upon as pulmonary senility; as hypothyroidism produces premature senility, emphysema is the senile change in the lung corresponding to the graying of the hair. The oppression of respiration is often accompanied by palpitation and lancinating pains over the region of the



FIG. 72.— Before treatment.      FIG. 73.— After 10 months' treatment.  
Incomplete Myxedema.

heart, resembling angina pectoris. There is often dilatation of the left heart and aortic insufficiency, the result of the increased mean blood pressure from the contraction of the arterioles and capillaries of the skin.

The venous system suffers from the premature senility, varices, varicoceles and hemorrhoids are common, the veins in the back of the hands are dilated, even in the young and sometimes on the anterior surface of the thorax. The capillary system suffers with the rest of the vessels, as shown by the dry, harsh desquamatory condition of the skin; the red patches on the cheeks, the condition of the

gums and mucous membranes. Of the changes in the arterial system the loss of tonicity is the most marked.

The liver often becomes congested. Ver Ecker has shown that thyroidectomized animals have a marked congestion of the liver; Berkeley observed a general passive congestion of the organs in mice poisoned by thyroid feeding. In mild cases the liver is simply enlarged, in more advanced cases the patients complain of a weight in the hepatic region; there is also pain over the gall bladder and gall stones are frequently present.

The symptom which seems to predominate in all cases of hypothyroidea, whether in cretinism, myxedema or in the incomplete forms, is obstinate constipation; to this the patient often ascribes all her ailments.

Amenorrhea and dysmenorrhea are the rule; there is also retroflexion of the uterus even in the young, due to imperfect development of the posterior wall of the uterus, fibromas are often present, to the retroflexion and the fibromas the gynecologist ascribes all the symptoms, but operation fails to relieve the patient. Impotence and loss of sexual desire are a common cause of patients seeking advice.

Owing to the increased activity of the gland during pregnancy the patient is often in better health during this period, the extra secretion being utilized by the maternal system, often to the detriment of the fetus. During this period many of the symptoms disappear entirely and the patient becomes normal, but at the end of lactation she relapses and is generally worse than before. The first symptoms may appear after one or more pregnancies, if the patient's bowels have been regular before and become constipated after pregnancy, or if the menstruation becomes abnormal; it is well to look further for evidence of hypothyroidea, especially should the patient who previously was active and energetic become languid and apathetic regarding her household duties.

When the disease is fairly advanced the patients become somnolent, fatigued, languid and apathetic, everything to be done appears to be above their physical and moral strength. They complain of feeling unnatural.

The heart's action is feeble and the second sound accented, or there may be aortic valvular insufficiency, the pulse is slower than normal and the temperature may be subnormal; there is often a feeling of depression, which appears to the patient to emanate from the cardiac region. The erythrocytes are decreased as is the hemoglobin. There is often a tendency to hemorrhage, slight injuries bleeding freely, epistaxis may occur and postpartum hemorrhage has to be guarded against. These latter symptoms are due to the increased blood pressure and the reduced coagulability of the blood. In the urine there may be albumin and casts due to the venous congestion of the kidneys. I have rarely found kidney insufficiency in these cases, the freezing point of the urine being within normal limits, serum albumin and serum globulin are rare though nuclealbumin is not uncommon. The nitrogen elimination is low. Byrom Bramwell has noted large quantities of mucus in some of his cases. In the urine oxalic acid is often in excess, phosphoric acid is low, neutral sulphur is high, being often 25 per cent of the total sulphur. Chlorids are high in proportion to the nitrogen. There is an excess of ethereal sulphates, indican and skatoxyl being in excess, due to the constipation. The proportions of the nitrogen eliminated are pathologic, the urea nitrogen may be as low as 65 per cent of the total nitrogen, ammonia nitrogen 6 to 7 per cent or even higher. The uric acid nitrogen low or normal, the residual nitrogen is often very high. The carbon nitrogen factor is usually high; urobilinogen is in excess, bile pigments present in traces and sometimes indoxylglycuronic acid.

The stomach usually shows a hypo- or anachlorhydria.

The latter is rare; there is an excess of mucus and organic acids.

There are also certain mental changes which may amount to insanity, sometimes melancholic, at other times maniacal or simply delusional. These cases will be considered later.

The multiplicity and complexity of the symptomatic picture calls for the most careful examination by the physician, and even then he is often compelled to make a diagnosis by exclusion.

*Treatment.*—The treatment of all forms of myxedema is the same, viz: the administration of the thyroid gland of some animal, that of the sheep usually being employed.

Since the discovery of Murray, in 1891, that myxedema could be successfully treated by subcutaneous injections of an extract of the thyroid gland of the sheep, and the further advance of Howitz, of Copenhagen, and Mackenzie and Fox, in 1892, that the administration of the thyroid by the mouth was equally efficacious the disease is no longer looked upon as beyond relief. If the patient is suffering from abolition of function of the thyroid gland alone with no complications thyroid feeding is a specific, and no case will fail to be improved or cured by its use. There are cases which apparently do not react to thyroid treatment in which there is some complicating disease, or the disease has produced a dementia from which there is no recovery. In other cases the treatment fails from the nonabsorption of the drug. The active principle of the gland is not absorbed from the stomach, it being only soluble in alkaline solutions and is precipitated by organic and inorganic acids. Should the intestinal tract of the patient be acid throughout its whole length, a condition which must be not uncommon in these cases, with whom obstinate constipation and intestinal putrefaction, producing fatty acids in quantity, is a constant condition,

there would be no absorption of the drug. It is, therefore, necessary that in all cases attention should be paid to the condition of the digestive tract. The administration of natrium bicarbonate in five or ten grain doses and two or three grains natrium sulphate in a tumbler of water about thirty minutes before meals washes out the stomach, neutralizes the fatty acids and helps to relieve the constipation, the sulphuric acid of the sulphate combining with the phenols formed in the colon, rendering them innocuous. The desiccated thyroid gland, preferably that manufactured by Armour & Co., should be given in one grain doses three times a day and gradually increased to three grains; it is rarely advisable to go above this dose, though occasionally five grains is borne without producing symptoms of thyroidismus. It should always be administered with caution, especially in those cases where the heart is weak, or the arteries degenerated, and it should be withdrawn on the first symptoms of thyroidismus, commencing again in a few days with a smaller dose.

The addition of a little strychnia and arsenious acid have a decidedly beneficial effect. For the constipation there is nothing equal to sodium glycocholate mass and magnesium oxid. From three to five grains of each will, after a week or two, make the bowels act regularly.

Where the mental depression is severe the addition of one grain of opium to each dose of the thyroid will act as a heart stimulant.

In children the dose should never exceed two grains a day to commence with, and it is better to begin with one, gradually increasing it according to how it is borne. In children the alkali treatment is of as much or more importance than in the adult; strychnia and arsenic are useful adjuncts in children but the use of opium requires caution. The glycocholate of soda and magnesium oxid are not adapted for children unless they can swallow a capsule; the



taste of the glycocholate is too nauseous to be administered in solution; liquorice will disguise the taste fairly well.

Should there be dilatation of the heart or if the skin symptoms are severe, the Shott baths are a very useful adjunct; when given at night they produce refreshing and prolonged sleep.

The diet should be plain and substantial, calculated to assist in relieving the constipation.

## CHAPTER XIII.

### BASEDOW'S DISEASE.

Basedow's disease, exophthalmic goitre, or Graves' disease is one of the most interesting of diseases on account of the peculiarity of its symptoms and the mystery of its etiology and pathology. It was first described in 1835 by the celebrated Dublin physician Graves, and in 1840 Basedow gave a complete and elaborate account of its clinical features. Since that date the literature on the subject has reached enormous proportions, as can be gathered from Albert Kocher's monograph on the surgical treatment of the disease, which contains no less than 1423 references.

Basedow's disease, like myxedema, is much more common in women than in men, the proportions varying from 5 to 10 to 1 according to different authors and the age from 14 to 60 years, with the majority of cases between 20 and 40. Unlike myxedema marriage and childbearing seem to have little effect in this disease, the preponderance of cases occurring in married women, though Byrom Bramwell, in his list of 79 cases, found 47 were single and 26 were married or widows.

Direct heredity, viz: that the parents had Basedow's disease and that it descended directly to the offspring has, so far as I can find, never been observed; occasionally more than one member of a family is affected. There are many cases recorded where the parents or near relatives have been affected with some other form of nervous disease, or that there is some history of general nervousness, hysteria, epilepsy or insanity in some more or less remote relation. The weakness of the argument in favor of heredity in this and many other diseases, is shown by the

list of cases which Byrom Bramwell cites as evidence of the heredity of the disease; out of 79 cases he finds that in one case a sister had a large goitre, in one case an aunt had Basedow's disease, in one case a cousin, two cases were sisters, and in another case the patients were sisters. In these six cases out of a total of 79 only one case can be



FIG. 74.—Basedow's disease.

attributed to heredity and that was from an aunt. Exhaustion from acute illness, especially influenza or loss of blood, seems to be an exciting cause. Peripheral irritation in the nose and in the abdominal and especially pelvic viscera is also an exciting cause; many cases are on record where ovarian or uterine troubles were associated with symptoms of Basedow's disease, and that after laparotomy the symptoms disappeared, which may be accounted

for by the connection of the thyroid with the organs of generation. Anemia seems to play a part in the causation of the disease. Nervous shock, profound mental anxiety and fright seem to have some effect upon its causation, though more often a symptom rather than a cause. Many of the symptoms and the facial expression are identical with those of fright.

The etiology of Basedow's disease is as yet unsettled. Though many theories have been brought forward at various times by different observers none have received general acceptance. Basedow considered that the disease was the result of a primary change in the blood, but recent investigators have shown that the red corpuscles and the hemoglobin are usually normal in amount and when anemia occurs it is due to starvation from continued vomiting. Stokes was of opinion that the cause of the disease was a heart lesion. Lemke attributed it to a disease of the muscle of the heart and Askanazy found histological changes in the muscle tissue in many cases. Jakob claims that these muscle changes are of toxic origin but it is more probable they are due to an abnormal metabolic condition. Disease of the pelvic viscera has from time to time been observed associated with this disease, the symptoms disappearing after operation on the pelvic lesion. Enteroptosis, diseases of the nose, floating kidney and autointoxication have all had their advocates. Renaut described the cirrhosis of the thyroid gland and claimed that an imperfect lymph circulation was the cause, which was supported by Müller, who pointed out that the lymph glands of the neck are swollen; presumably the thyroid was unable to eliminate its colloid into the lymphatics, which would cause swelling of the gland, with possibly a change in the colloid substance and also necessitate its elimination into the blood vessels. Charcot and Baschan claimed that the disease was primarily due to

alterations in the ganglion cells of the cortex. Ballet considers the disease as a bulbar neurosis and von Cyon as a lesion of the depressor cordis.

Several writers agree that the symptoms are the result of an irritative lesion of the sympathetic. Pathologists, however, have been unable to find any constant lesion in the ganglia either of the neck, thorax or abdomen. There being no marked or constant dilatation of the pupils argues against the disease being of sympathetic origin; on the other hand, the dilatation of the blood vessels, which is a constant condition, may very well be due either to a paralysis of the vasoconstrictor or irritation of the vasodilator fibres of the sympathetic. Pressure on the sympathetic of the neck by the enlarged gland is also said to cause the disease, and some cases have recovered after section of the sympathetic of the neck. Frederick suggested that there might be a paralysis of the vasomotor nerves which would cause a dilatation of the coronary arteries, thereby increasing the excitability of the cardiac ganglia causing increased action of the heart. Lesions in the nuclei of the pneumogastric nerve and other structures in the medulla oblongata have been found but nothing that was not probably secondary in its origin. E. Zeddeschi implicates the restiform bodies. He states that lesions of the anterior portion of the restiform bodies in animals produce marked symptoms of Basedow's disease; further that animals in whom the symptoms of Basedow's disease have been induced by lesions of the restiform bodies and when such symptoms have been diminished or have disappeared they may be reproduced wholly or in part by feeding with thyroid to the point of hyperthyroidism. He further states that lesions of the restiform bodies in thyroidectomized animals do not cause symptoms of Basedow's disease. In animals in whom the symptoms of Basedow's disease have been induced through lesions

of the restiform bodies removal of the thyroid diminishes or causes the disappearance of the greater part of such symptoms. These latter experiments, if confirmed, are of great importance.

Möbius has strongly advocated the theory that the primary cause of the disease is hypertrophy and hypersecretion of the thyroid gland. Greenfield and George Murray support this view, the latter arguing that the gland in Basedow's disease is to be compared to the mammary gland during lactation. The enlargement of the thyroid is one of the chief symptoms and even when comparatively slight there is an increased circulation through the gland, producing a hypersecretion which must necessarily find its way into the circulation. Many of the symptoms of Basedow's disease are the exact opposite of those of myxedema, which is admittedly the result of absence of thyroid secretion; further, it has been observed that Basedow's disease may develop into myxedema on the subsidence of the swelling, due to atrophy of the gland; while the converse, viz: myxedema developing into Basedow's disease has never been recorded and more conclusive still is the fact that partial excision of the enlarged gland has often been followed by improvement and cure of the disease. Edmunds has produced exophthalmos, tumor, etc., by feeding thyroid to monkeys, and cases are on record where the symptoms have developed in man from overdosing with thyroid extract.

In the following table the symptoms of myxedema, Basedow's disease and thyroidismus are placed in parallel columns, so that the antagonistic symptoms as well as those which are common to both can be easily compared:

| <i>Myxedema.</i>   | <i>Basedow's Disease.</i>  | <i>Thyroidismus.</i>                               |
|--|--|--|
| Absence or atrophy of the thyroid gland.                               | Diffuse swelling of the gland, hypervasculation, hyperplasia.                        |  |
| Slow, small, regular pulse.  | Rapid, dilated, sometimes irregular pulse.   | Rapid, dilated, weak pulse.                        |
| Torpid, stolid, stupid expression.                                     | Anxious, unsteady expression; when the gaze is fixed fierce expression.              |  |
| Narrowed fissure of the eyelids.                                       | Widened fissures of the eyelids, exophthalmos.                                       | Widened fissures of the eyelids, exophthalmos.     |
| Slowness of digestion and excretion, poor appetite.                    | Abundant excretion, generally abnormally large appetite.                             | Abundant excretion.                                |
| Reduced metabolism.  | Increased metabolism.  | Increased metabolism.                              |
| Thick, opaque, flabby, dry, scaly skin.                                | Thin, transparent, injected damp skin.   | Damp skin.   |
| Fingers short and thick, often spadelike.                              | Long, slender fingers with pointed ends.   |  |
| Drowsiness and somnolence.   | Insomnia and disturbed sleep.  | Nervousness, irritability.                         |
| Slowness of perception and decreased sensation and action.             | Increased sensation, perception and action.  |  |
| Slowness of thought.   | Rapidity of thought, psychological disturbances, hallucinations, mania, melancholia. |  |
| Want of activity and slowness of motion.                               | Continuous activity and rapidity of motion.  |  |
| Stiffness of the extremities.  | Trembling of the extremities, increased motility of the joints.                      | Paralysis of one or more limbs, muscular weakness. |
| Arrested development of the bones, short, thick, often deformed bones. | Slender skeleton, here and there soft and thin bones.                                |  |
| Continuous feeling of cold.  | Unbearable feeling of heat.  | Flushings, feeling of heat.                        |
| Slow difficult breathing.  | Superficial breathing with defective inspiratory expansion of the chest.             |  |
| Increase of body weight.   | Decrease of body weight.   | Decrease of body weight.                           |
| Premature aging.   | Youthful appearance in the commencement of the disease.                              |  |
| Electrical resistance of the skin diminished.                          | Electrical resistance of the skin increased.   |  |
| Temperature subnormal.   | Temperature normal with occasional increase.   | Temperature increased.                             |
| The bowels constipated.  | Diarrhea the rule.   | Diarrhea the rule.                                 |

| <i>Myxedema.</i>   | <i>Basedow's Disease.</i>  | <i>Thyroidismus.</i>   |
|--|--|--|
| Thyroid feeding cures.   | Thyroid feeding usually increases symptoms.  |  |
| Skin dry, cold, sweating absent.   | Sweatings, flushings, tremors, palpitation, increased pulse.   | Sweatings, flushings, tremors, palpitation, increased pulse. |
| Characteristic edema of the skin.  | A characteristic edema.  |  |
| Loss of the hair of the head and eyebrows usually not complete.                      | Loss of the hair of the head and eyebrows often complete.  |  |
| Dryness of the hair, single hairs thick and rough.                                   | Hair dry, single hairs thin and rough.   | Hair becomes dry and falls out.                              |
| Loss of hair rarely complete.  | Loss of hair often very extensive.   |  |
| Pigmentation of the skin yellow to brown, seldom dark, affects the whole body.       | Pigmentation of the skin generally brown, often in patches, resembling Addison's disease.                |  |
| Pigmentation usually most marked on eyelids, forehead, face, lips, nose and breasts. | Pigmentation usually most marked on eyelids, forehead, lips, breasts, axillæ, region of umbilicus, neck. |  |
| Reduced secretion of saliva.   | Reduced secretion of saliva seldom.  |  |
| Reduced tear secretion rarely increased.   | Reduced tear secretion often increased.  |  |
| Want of feeling in the extremities common.   | Want of feeling in the extremities seldom.   |  |
| Tiredness in the legs.   | Tiredness mostly very marked in the legs.  |  |

The symptoms which are directly opposite, are more numerous and more important, while those in which the two diseases resemble one another are principally in connection with the skin. The edema of Basedow's disease is, however, hardly the same as the pseudoedema of myxedema. The former is often an irregular condition appearing in various parts of the body, rapidly disappearing, and which is described for want of a better term as "nervous edema." In both diseases there are the lipomatous swellings in the supraclavicular region and elsewhere, but they are by no means so common in Basedow's disease as in myxedema. The swelling of the lips and



tongue is apparently the same, but in myxedema it is probably due to the pseudoedema, while in Basedow's disease it is the result of a congestion. As Basedow's disease often passes into a myxedema as the result of the atrophy of the thyroid gland those symptoms which are the same in both diseases may be really the first symptoms of the myxedematous cachexia. The fact that many cases of Basedow's disease are improved by the administration of thyroidin or phosphoric acid goes to show that in some cases there is a pathologic condition of the thyroid secretion and suggests the possibility that, in spite of the apparent hypersecretion of the gland, there may be an absence of normal secretion producing myxedema, or possibly that the gland possesses a double function, one of which may be perverted or lost while the other is increased or normal. Recently Ecker, Faure, v. Jaksch, Mackenzie and others have observed symptoms of tetany in long standing cases of Basedow's disease or after operation. It is possible that these symptoms may be the result of lesions of the parathyroids. Others again claim that Basedow's disease is primarily a disease of the parathyroids and, it is claimed, that good results have been obtained by parathyroid feeding. It seems not improbable that some of the symptoms at least may be due to a pathologic condition of these glands.

The theory that the hypersecretion of the thyroid gland is the principal factor in the production of the symptoms of Basedow's disease has been confirmed by the recent experiments of Edmunds, detailed in a previous chapter. He was able to produce many of the symptoms in monkeys by thyroid feeding, and Notkin reports the case of a patient which was diagnosed as a case of Basedow's disease, it being subsequently discovered that he had been taking enormous quantities of thyroid for obesity. M. Gagnevin, a healthy medical student, took full doses of

thyroid for eight days under the supervision of Dr. Combe, of Lausanne, and suffered from palpitation, increased frequency of heart's action, tremors, sweatings, flushings and exophthalmos.

#### ETIOLOGY.

The arguments against the theory of the hypersecretion of the thyroid gland being the cause of Basedow's disease are clinical rather than scientific. It is argued that the former theory is based upon two postulates. First, that the symptoms produced by large doses of thyroid are similar to the symptoms of Basedow's disease. Second, that the symptoms of myxedema the result of hypothyroidia are largely the antitheses of Basedow's disease.

As to the first point it is argued that an atypical Graves disease is not produced by thyroid feeding but only a few symptoms which simulate but are not identical with those of Basedow's disease and that the same symptoms can be produced by the continued administration of other animal extracts, especially the parotid, that the symptoms produced by thyroid feeding resemble those of overdoses of the nitrites and allied drugs.

On the second point it is argued that though the symptoms of hypothyroidin as seen in myxedema are the opposite of those of Basedow's disease it by no means necessarily follows that the latter disease is the result of hyperthyroidia and further that there is no other known example of a specific disease due to hypersecretion on the part of any gland whatever. Hypersecretion of any gland as far as is known is the result of some agent in the blood and not of the gland's self-excitation. In parenchymatous goitre a blood poison is undoubtedly present which the gland had no share in producing, however much the gland may be affected.

The objections to the theory of hypersecretion of the thyroid being the cause of Basedow's disease are worthy

of great consideration. The severity of the symptoms of Basedow's disease bears no relation to the degree of thyroid hypertrophy which may reasonably be taken as a fair index of hyperactivity. The thyroid enlargement differs materially from parenchymatous goitre in being variable in size and even disappearing with no corresponding change in the general symptoms, the size of the thyroid is further no indication as to the severity of the disease, and that all the symptoms of severe Basedow's disease may occur in cases where the thyroid is not palpably enlarged as in the so-called masked cases described later.

From the above it is argued that the enlargement of the thyroid is a secondary and not a primary element in the etiology of the disease, the result of overstimulation of the normal function of the gland or neutralizing certain blood poisons generated during digestion in excess.

The results of feeding in thyroidectomized animals described in a former chapter has led to the conclusion that the function of the gland is intimately connected with the digestive processes and therefore that a marked change in the gland or its secretion may be caused by digestive disturbances. Thompson in his work on Graves' disease strongly advocates the digestive etiology of Basedow's disease and cites cases of cure or improvement in which the treatment has been entirely dietetic with relapses when the regimen was neglected.

In weighing up the etiologic theories of Basedow's disease it must be remembered that spontaneous enlargement or hypersecretion of the gland is more than improbable, that toxemia in some form or another is the cause of nearly all disease, that the functions of the thyroid are intimately connected with metabolism and assimilation and that the chemical evidence of hyperthyroidea being the cause of the disease is by no means complete. From the evidence at our disposal the etiology of Basedow's disease may be

summed up to be due to an excessive or perverted secretion of the thyroid gland, the result of a toxemia probably produced in the digestive processes.

The prognosis in Basedow's disease is a matter of great uncertainty. Usually the disease runs a chronic course, with intermissions of temporary improvement. In a few cases the disease subsides spontaneously, but as a rule the cure is far from complete, the symptoms subsiding to a certain point and remaining stationary followed by severe relapse. Rarely the disease begins suddenly and subsides rapidly. In other cases the disease progresses more or less slowly, but steadily, terminating in death. In those cases where the patient dies from the disease itself and not from some intercurrent complication death is gradual but occasionally sudden.

There are five cardinal symptoms of Basedow's disease, increased action of the heart, enlargement of the thyroid gland, prominence of the eyeballs, tremors, nervous irritability or a condition of general nervousness, besides which the following symptoms may be present:

*Cardinal Symptoms.*—Increased action of the heart, palpitation, throbbing of the vessels, etc.,  
 Enlargement of the thyroid,  
 Prominence of the eyeballs,  
 General nervousness,  
 Fine rhythmical vibratory tremor.

*Digestive Organs.*—Diarrhea,  
 Vomiting,  
 Loss of appetite, bulimia, sudden fits of hunger,  
 Thirst,  
 Jaundice.

*Respiratory Organs.*—Cough,  
 Increased frequency of respiration,  
 Diminished inspiratory expansion.

- Nervous System.*—Von Graefe's symptom,  
Stellwag's symptom,  
Defective convergence (Möbius),  
Ophthalmoplegia externa,  
Paralysis, a peculiar form of paraplegia,  
Epileptiform convulsions, chorea,  
Headache, neuralgia, angina pectoris,  
Psychical derangements, depression, mania, etc.
- Integumentary System.*—Sweatings, flushings, sensations  
of heat, rises in temperature,  
Diminished electrical resistance,  
Increased pigmentation,  
Leucoderma,  
Loss of hair, atrophy of nails.
- Urinary System.*—Polyuria,  
Albuminuria,  
Glycosuria,  
Hyperazoturia,  
Phosphaturia, (?)  
High uric acid.
- Generative System.*—Menstrual derangements,  
Loss of sexual desire, impotence.
- General.*—Debility, loss of weight, anemia, cachexia,  
edema of lower extremities.

Murray and Kocher are very decided in their statements that without enlargement of the thyroid gland Basedow's disease cannot exist, and in my experience this is true in the very great majority of cases. I am, however, convinced that cases do occur where there is probably a very marked hypersecretion of the gland without any palpable enlargement; that the enlargement of the gland may be posterior or that the hypersecretion may be due to accessory glands is possible; the palpation of the gland is admittedly attended with difficulty, and any slight enlarge-

ment may easily escape detection. Byrom Bramwell claims that in 10 of his 79 cases thyroid enlargement was absent.

In a typical case the size of the gland may vary from being hardly palpable by the practiced diagnostician to the size of a goose egg, in which cases the isthmus and the pyramid and the accessory glands are also enlarged.

The enlarged gland is of variable consistence, depending upon its vascularity. It is usually firm and elastic if the swelling is of some duration. If examined soon after its appearance it may be soft and not uniform, some parts not being vascular, but firmer and harder than others. It is rare that the hyperplastic struma, the common form, presses on the trachea sufficiently to produce dyspnea; the dyspnea when marked is of cardiac origin. The vascular struma, or, as Kocher prefers to call it, the teleangretoid struma, is characteristic in its symptoms.

The circulatory changes in the enlarged gland are usually very apparent, the gland pulsates in a manner suggesting aneurysm, sometimes combined with a lifting movement of the whole gland, due to the pulsations of the carotids. The gland can be compared to an elastic capsule filled with enlarged vessels, through which the blood stream is passing with abnormal rapidity on account of the increased heart's action, producing a marked diastole followed by a systole. So great is the dilatation of the vessels in severe cases that the arteries can be seen to pulsate and the branches of the superior thyroid artery can be traced through their tortuous course on the surface of the gland by palpation. The veins of the gland sometimes pulsate, as do also the large vessels of the neck. In severe cases the pulsation of the gland veins is a negative pulse, due to the dilatation of the vessels, the increased circulation and the weakness of the vessel walls.

On auscultation there is a distinct blowing murmur

present over the gland and vessels, the intensity of which varies with the severity of the disease; it is short or long and sometimes continuous, systolic in point of time, and when continuous is emphasized in systoles. It is best heard over the trunk of the arteries, especially in the superior thyroid arteries; should the *arteria ima* or *pyramidalis* be present the murmur can be heard over them. The murmurs are not usually heard over the whole gland, but only in places; where vascularity is most marked compression of the gland usually increases the murmur.

Combined with the murmur is another symptom which is often present, viz: a friction thrill which can be felt on palpation occasionally over the whole gland, but usually only in the vascular portions and over the artery where the murmur is loudest. Both the murmur and the friction sound are due to the rapid circulation and to the swirl of the blood stream as it passes from a narrow into a wider vessel.

The vessels are very much enlarged, especially those arteries which supply the vascular portion of the struma; if the whole gland is affected then all four arteries are dilated, as are also the *arteria ima* and *pyramidalis* when present. Should the hyperemia be reduced the arteries will return to the normal size, providing the case is not one of too long standing. Hand in hand with the increase of the arteries goes an increase in the size of the veins, but often not to the same extent, the veins being full and only in severe cases dilated. Occasionally when the struma is compressed, owing to its being extended into the upper opening of the thorax, the veins of the throat and the superficial veins of the breast become dilated. In long standing cases the jugulars may become dilated. The walls of the veins and arteries become thin and weak, which cannot be diagnosed clinically, but is a point to be remembered during a surgical operation. The micro-

scopical examination of the walls of the vessels show a reduction of the elastic fibres and a space between the intima and adventitia.

Another symptom is that the struma can be partially emptied of blood by pressure, returning to its original size as soon as the pressure is removed. It is improbable, according to Kocher, that pressure on the gland causes an increased outflow of colloid into the system, which many operators consider the cause of occasional sudden fatal results from operative procedures. In many cases the patients have themselves on several occasions reduced the goitre by pressure without any untoward results.

The etiology of the hypervascularity of the gland and the enervation of the vessels must be connected with the primary cause of the disease. A vessel nerve degeneration has been recorded by Guttman and Gerhardt but why the nerves of the thyroid vessels should be especially attacked is a question which cannot yet be answered.

The heart fluctuates in size in the majority of cases and is dilated in about 30 per cent, depending on the severity of the disease. Tachycardia is one of the cardinal and most pronounced symptoms of the disease which is always present, and may vary from 90 to 250 pulsations per minute and in some cases is arrhythmic; attacks of angina pectoris are not uncommon; the apex beat is diffuse and increased in force; in severe cases the whole of the cardiac area pulsates visibly, the pulsation passing along the main arteries producing a marked epigastric pulsation. In very severe cases the whole thorax may pulsate while the patient is at rest, being so severe as to produce movement of the head. Palpitation may also be very severe but is by no means a constant cause of complaint; it is usually the first symptom of which the patient complains and is constant, fluctuating in degree, being usually more severe in the morning.



The heart sounds are accentuated but an abnormality can seldom be detected. Murmurs and friction sounds are common, varying with the irritation and rapidity of the heart, but valvular insufficiencies can rarely be detected.

As stated above, the pulse is rapid, and throbbing of the vessels in the head and neck are often complained of, causing great discomfort. The pulse is usually small in size and regular; at times it is dicrotic and in the latest stages of the disease it may become irregular or intermittent. Besides the murmurs heard over the vessels of the neck, murmurs can occasionally be heard over the smaller arteries, as the brachial and crural; there is a distinct capillary pulse. Hemorrhage, epistaxis, bleeding of the gums, pulmonary hemorrhage may occur. Varicose veins and hemorrhoids are common. Becker's retinal pulse and Gerhardt's liver and spleen pulsation have been occasionally observed. In long standing cases edema of the feet and ankles may occur.

Prominence of the eyeballs, exophthalmos, which is usually bilateral, rarely unilateral, is one of the most prominent symptoms, being rarely absent in well marked cases. When the exophthalmos is marked and the upper lid spasmodically contracted, as sometimes happens, there is a typical staring look which gives a fierce or frightened expression to the face. So great may be the protrusion of the eyeballs that the recti muscles become visible, and cases are on record where the eyeball has become dislocated from the orbit and had to be replaced with the finger. The exophthalmos varies according to the emotional condition of the patient, any excitement causing it to increase. A school teacher stated that she first became aware of the exophthalmos by her pupils becoming frightened by her appearance; this no doubt was partially due to the normal retraction of the lid which takes place during excitement. The protrusion may be so great that the

eyelids are unable to close over the eyeball, producing conjunctivitis and ulceration of the cornea, but as a rule the eyesight is but little affected, the retinal vessels are dilated and occasionally pulsate. Spasm of the fibres of Müller's muscle and the accumulation of fat behind the eye in the orbit, with dilatation and engorgement of the vessels back of the eye are often given as causes. The pupils are usually normal, but may sometimes be dilated, they may be unequal; the absence of any marked change in the pupils seems to oppose the theory that the exophthalmos is due to a lesion of the sympathetic. Stellwag's sign is the contraction of the upper lid, which is probably due to spasm of Müller's muscle. The spasmodic contraction of the lid varies in degree and causes the aperture between the lids to be wider than normal. This is not a constant symptom, but is of importance, though it has been observed occasionally in cases where Basedow's disease did not exist. Absence of blinking occurs in about 5 per cent of the cases. Von Graefe's sign consists in the upper lid failing to follow the eyeball in a steady coördinate manner, the lid only following the downward movement of the eyeball in irregular jerks. This symptom can be observed by fixing the patient's gaze on an object above the level of the eye and slowly lowering the object towards the ground, when the failure of the lid to follow the eyeball can easily be seen. This symptom is present in about 50 per cent of the cases. Möbius' symptom consists in the patient being unable to converge for near objects and is present in about 25 per cent of cases.

One of the most constant and important symptoms is the muscular tremor first described by Marie and Charcot, consisting of fine rhythmical tremors about eight or nine to the second or twice as rapid as the tremors of paralysis agitans. The muscles usually affected are those of the upper and lower limbs, though occasionally the whole body

trembles and can be felt by placing the hand upon the shoulder. Charcot mentions that the individual digits do not tremble, which he claims distinguishes it from the tremor of alcoholism and the general paralysis of the insane, in which conditions the tremor is equally rapid. Occasionally the tremor is unilateral. It can be observed best by extending the arm at right angles to the body and placing a pencil between the fingers. In a certain proportion of cases there is an irregular spasmodic jerking of the fingers and toes. The tremor usually does not appear till the palpitation has become marked; it is a symptom of great value in diagnosing cases of masked Basedow's disease, which will be described later.

The nervousness of the patient is a very marked symptom, contrasting with the apathy and torpor of myxedema. There are a number of what may be termed "simple" psychic symptoms, more or less marked, connected with Basedow's disease which can be broadly classed under the headings of psychic instability and irritability with the want of continuity of ideas resembling hysteria or neurasthenia; occasionally true hysteria or neurasthenia are associated with Basedow's disease but the majority of cases do not present the stigmata associated with true hysteria and neurasthenia and are a part of the symptom complex of Basedow's disease.

Sooner or later after the onset of the disease the character of the patient changes, he becomes irritable, selfish, peevish, exacting, intolerant of contradiction, never satisfied and never recognizing the sacrifices made for him by others; at times he may have periods of most enthusiastic gaiety, changing almost suddenly to bitterness and melancholic depression. Generally they have an abnormal activity, a desire to continually change their position, an irritability of desire, a feeling of desire, but not knowing what it is they want, they are tormented by an indefinable,

incessant desire for change; at one moment taciturn and reserved, they almost suddenly become loquacious, speaking with a singular and apparently forced volubility, supporting theories contrary to their normal views with spasmodic energy, often almost fiercely, forgetting the courtesies of argument and at the slightest contradiction becoming rude and irate. In time these psychic symptoms which have been happily described as "psychic chorea" become accentuated, the patient may suddenly develop a most marked aversion for some member or members of the family without any apparent reason which no amount of explanation or argument can overcome. More rarely the patient is habitually depressed, continually occupied with the contemplation of his own troubles he becomes taciturn and morose; as a rule Trousseau's description, "*la maladie de Basedow est une colère perpetuelle,*" is correct.

Insomnia and nightmares are almost invariably present, adding to the mental and nervous instability; the memory becomes defective in chronic cases, details escape and become mixed, scientific data and words of a foreign language are the first to be forgotten; in severe cases the memory may become so defective that the patient forgets what he has read only three or four lines above, making reading valueless.

Will power is as a rule not affected; it may be diminished and very rarely abolished. In most cases, however, the patient is changeable, forming different and often contradictory resolutions at short intervals.

These psychic symptoms become more and more accentuated, the patient at times passing the border line and becoming insane. Many observers have considered the occurrence of insanity in Basedow's disease as a coincidence, each disease developing separately and from separate pathologic conditions, arguing from the insanity

being of various kinds—hysteria, epilepsy, alcoholism, mania and melancholia—which progress finally to dementia.

The theory of the duality of the disease is not borne out by clinical examination; insanity may develop for the reason that the nervous and mental condition is enfeebled, but it is by no means uncommon for the insanity and Basedow's disease to develop at the same time, the insanity subsiding with the other symptoms. In some cases of insanity the Basedowic symptoms develop only after some time, in which case they may have been latent, masked or incomplete and have been the primary cause of the insanity, or they have developed independently of the insanity.

The form of insanity supervening in Basedow's disease is most frequently depressive mania, exaltation rarely occurring, melancholia and delusions of persecution resembling paranoia. In a case diagnosed as paranoia which came to autopsy the thyroid was found much enlarged, weighing 94 grams, though no enlargement had been observed during life.

The insanity of Basedow's disease is attributed by Hirschl to changes in the cerebral circulation (probably the cause of all the insanities). Jacquim considers it due to the emaciation and weakness when the nutrition is poor and the continued vomiting and insomnia have weakened the nervous system. In his opinion insanity plays the same rôle in Basedow's disease as delirium in typhoid fever. Most observers ascribe the mental symptoms to the diseased condition and hypersecretion of the thyroid.

Direct experiment upon the human as to the effect of excessive thyroid feeding on mentality is of course impossible, but several cases are on record where mental symptoms have been produced by accidental overdosing with thyroid.

Dr. Boinet in the *Semaine médicale*, 1899, records the case of a man suffering from exfoliating general dermatitis who took large doses of thyroid, followed by palpitation, trembling of hands, increase in size of thyroid, with psychic symptoms of delusions of persecution and mental confusion, which disappeared on the treatment being suspended. Dr. Ferrarini treated a woman for obesity with large doses of thyroid. She developed mental confusion, motor disturbances, depression, tremor and increased pulse rate; the symptoms disappeared on the suspension of the drug.

Headache is a severe cause of complaint, neuralgia is common, the condition as to sleep is variable, migraine, angina pectoris, epilepsy and chorea occur as developments during the disease. Charcot describes a special form of paraplegia which is peculiar to the disease. The paralysis is usually incomplete but may be absolute, the muscles are placid and atrophied, the reflexes, deep and superficial, are abolished, there are no twitchings, sensibility and electrical reactions are normal and the bladder and rectum under control. There is a sudden giving away of the legs, due to an unexpected flexion of the knees, which is characteristic of the condition. The paraplegia is functional and is not permanent; from the fact that there are no sensory disturbances it does not appear to be typical.

In a considerable proportion of cases of Basedow's disease there is developed a pigmentation of the skin distributed in patches or general, the genital organs, the areolæ of the nipples and around the orbits are usually darkest and may be the only places where the discoloration takes place. There is a peculiar dirty, dingy, yellowish brown appearance of the skin of the face and more or less of the whole body. The pigmentation in one form or another occurs in about 40 per cent of the cases, and where goitre

and exophthalmos are absent is of considerable diagnostic value. Patches of leucoderma, urticaria, eczema, erythema and other skin eruptions have been observed in about 10 per cent of the cases.

There is diminished electrical resistance of the skin, which is in marked contrast to the increased resistance in myxedema. This diminished resistance is probably due to the dilated capillary vessels which keep the epidermis bathed in fluid, the consequent sweating keeping the skin moist. Wolfenden found that the average electrical resistance of the normal skin was from 4000 to 5000 ohms, while in Basedow's disease he found it as low as 200 and in eight cases the highest was only 500 to 700. In alcoholism and akromegaly there is also a marked decrease in the electrical resistance, but not to anything like the extent as the above observations indicate.

The hair falls out and becomes thin in about 20 per cent of the cases and atrophic changes occur in the nails in a few cases; both these symptoms are probably due to the anemia rather than to the disease itself.

The respiratory symptoms are a short, deep, nervous cough, occurring in about 16 per cent of the cases; rarely a profuse pink watery secretion pours out from the bronchial mucous membrane. Increased frequency of respiration occurs, due to anemia, cardiac complication or is possibly of nervous origin. Bayson's symptom has been observed, viz: a diminished expansion of the chest during inspiration. Air hunger is common, the result of the anemia; there is also a weakening of the voice in a number of cases.

The lips are sometimes swollen and congested, bleeding easily, sometimes with a continuous tremor, which is increased while speaking; the tongue is swollen, the papillæ enlarged and of a bluish color, vibrating tremors are often present. There is a great increase in the secretion of the

saliva in some cases, in others the patients complain of dryness in the mouth and throat; often there is a difficulty in swallowing, rarely due to the pressure on the esophagus by the goitre but to the swollen condition and dryness of the mucous membranes of the mouth, pharynx and esophagus, which are of a bluish color; the gums are swollen, bleeding easily; the teeth are brittle.

In about 50 per cent of the cases there is vomiting, which cannot be ascribed to stomach derangements, as the secretions are usually normal or there may be a slight hyperchlorhydria. In some cases the vomiting is one of the first symptoms of which the patient complains; the vomiting may only take place in the morning when the stomach is empty, quantities of mucus being ejected which may be neutral or very slightly acid; the vomiting is sometimes so severe as to produce starvation, when the breath may have the sweet odor of acetone, diacetic acid appearing in the urine. It has been suggested that the vomiting of pregnancy is the result of the increased secretion of the thyroid.

Diarrhea occurs in about 50 per cent of the cases in sudden paroxysms without any apparent cause, persisting for several days and then disappearing; the evacuations are frequent, copious and watery, containing much mucus unattended by pain or colic, though in exceptional cases there may be colicky pains before an evacuation. There is said to be a very large elimination of phosphates in the feces. During an attack the tongue is clean and the appetite good or even voracious. Astringents are usually of little value, the diarrhea being of circulatory origin due to vaso-dilatation. The diarrhea, like the vomiting, may only occur in the morning, and in some cases is followed by obstinate constipation. Acholia is occasionally observed.

Excessive sweating is a very characteristic and constant symptom, combined with flushings of the face, hands, feet



or body with sensations of heat, but distinct rise of temperature is rare. The flushings and excessive sweating without increase of temperature are a valuable diagnostic symptom, occurring in about 90 per cent of all cases.

Enlargement of the lymphatic glands and spleen has been observed. In this connection it is interesting to note the frequency of persistence or regeneration of the thymus in this disease. Rendu, Johnstone, Hale White, Möbius, Marie, Joffroy, Schnitzler, Mackenzie and Edmunds, Gazonne and Murray have all pointed out the frequency of this condition. Bonnet reports 20 cases in which this abnormality existed, coinciding usually with a hyperplasia of the lymphatic tissues.

Loss of weight is usually a very prominent symptom. In severe cases not only does the panniculus disappear but the muscles are also affected. Very rarely a patient in spite of vomiting and nervous irritability will remain in good condition, sometimes even gaining in weight. The vomiting is probably the result of the increased thyroid secretion, as is perhaps also the vomiting of pregnancy. The loss of weight is accompanied by general weakness, until the patient is unable to do any work, and finally is confined to bed. A paraplegia already described results with the typical giving way of the knees. At the commencement of the disease there is usually a feeling of tiredness in the muscles which renders all exertion a burden.

Menstruation is usually decreased, though occasionally it may be profuse but is rarely normal. The mammae shrink as the disease progresses but there is not a distinct atrophy.

The urine is usually normal or slightly increased in quantity, even when polydipsia is present, the excess of fluid being eliminated by the skin. Glycosuria occurs in a few cases and albumin in small amounts is often present,

sometimes with casts probably of vasomotor origin. The urea and nitrogen are much increased, the phosphorus elimination is sometimes normal, usually much increased. Drechsel found that in patients taking considerable quantities of sodium phosphate there was no increase of the phosphates in the urine, probably they were eliminated in the feces; the uric acid was enormously increased in one case. Drechsel found 5.4 grms. in the 24 hours. This may be due to the cell destruction. The carbon nitrogen factor is low, oxalic acid is often slightly increased, the proportion of neutral sulphur is low, chlorids are usually low, bile pigment is often present, indol is generally above normal. In cases where there is starvation acetone and diacetic acid may be present.

There is a great aggravation of the cardinal symptoms immediately preceding death, the mental symptoms develop into an acute delirium requiring restraint, the temperature rises to  $103^{\circ}$  and  $104^{\circ}$ , the pulse and respiration are greatly increased. Vomiting, diarrhea, sweating, dermatitis, jaundice and convulsions may occur. The patient appears as if the victim of a nerve storm, some centres being more affected than others. The delirium consists in wriggling about the bed and refusing nourishment; severe hysterical-like delusions and hallucinations are common; rarely is there melancholia, the patient ultimately relapsing into a state of complete lethargy with rapid, catchy breathing. These final symptoms resemble death from removal of parathyroids.

The pathology of the thyroid gland in Basedow's disease has been the subject of very careful study by Achard, Askanazy, Brissaud, Edmunds, Ehrlich, Farner, Greenfield, Haemig, Horsley, Joffroy, Matheson, Möbius, Müller, Renaut and others with variable results. The most common form is parenchymatous hyperplasia of the gland, accompanied by structural changes and increased cell pro-

liferation, with changes of the colloid substance and of the stroma. These changes are characteristic of the tumor in the majority of cases, but Farner and Haemig describe a number of different forms of struma, most of which point to a chemical change in the secretion. It has been suggested that the colloid substance becomes qualitatively the same as the thyroid mucin, which is the sole constituent of the gland during fetal life. Ehrlich and Farner found the veins and arteries enlarged, also the capillaries were dilated and increased in number. Langhans considers that there is an increase in the number of follicles in nearly every case and that the contents are sometimes increased, sometimes diminished, there being apparently a qualitative change in the composition of the colloid substance. The changes in the protoplasm and nuclei of the cells are not constant but usually appear to be in the nature of a degeneration. He also found an excess of colloid in the lymph and blood vessels as well as in the stroma in the majority of cases. In a certain number of cases there is a mixed condition of parenchymatous hyperplasia and nodular formations. Struma nodosa is rare and when it occurs is probably the result of long standing disease. In the mixed form the nodules are usually typical, rarely developing into cysts, the hyperplasia is usually colloidal, seldom parenchymatous. Langhans found in the examination of 16 tumors that 8 were of the diffuse colloid variety, 6 partially colloidal and part parenchymatous, 2 wholly parenchymatous; the colloid substance being apparently normal. There is apparently no definite histological lesion of the thyroid in Basedow's disease. Lesions the same as those described above have been found in the thyroid glands of patients who exhibited no symptoms of Basedow's disease.

The question as to the increase, decrease or qualitative change of the colloid secretion in the disease is not yet

settled. Decreased secretion or rather a decreased quantity of the colloid substance in the gland has been often observed. Oswald, in his analyses of glands from cases of this disease, found a decreased percentage of iodine, but agreed that as the gland was increased in size the total be really increased. Farner's observation that the amount of thyroïdin might stroma, blood and lymph vessels contained an excessive amount of colloid points to an increased elimination with or without increased secretion. Haemig and Ehrlich are of opinion that the substance found in the stroma and vessels is either not colloid or at least not normal colloid, the latter considering that the changes in the colloid substance are due to the increased vascularity.

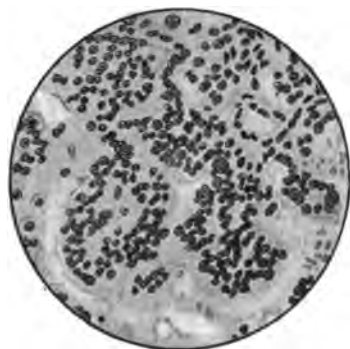


FIG. 75.—Thyroid gland in Basedow's disease.

That the tumor is due to increased vascularity there can be no doubt; the pulsation, the murmur and above all the fact that ligatures of the arteries cutting off the blood supply immediately reduces the size of the tumor, and that pressure on the gland reduces the size, it filling up again on removal of the pressure, place this point beyond question.

In the vessels themselves there is usually a thickening of the intima and a thinning of the media, the veins suffering in a like manner.

The lymphatic glands in the neck are usually enlarged and also those of the mediastinum, pointing to a pathological condition of the lymphatic system.

## INCOMPLETE BASEDOW'S DISEASE.

As there is an incomplete myxedema so there is an incomplete Basedow's disease, which is the result of a hypersecretion of the thyroid gland and consequent thyroidism. These cases vary from the typical with all the cardinal symptoms to what appears at first sight to be simply nervousness. The tremor is nearly always present to a more or less marked degree, combined with a pulse rate of 90 or above; the patient usually gives a history of having lost weight rapidly, which she ascribes to her nervous irritability, the least contradiction or annoyance throws her into a state of excitement; fear is usually the most marked symptom, which may resemble paranoia or delusional insanity. The appetite is poor, amounting in some cases to absolute refusal of all food, often accompanied with vomiting of mucus. There may be occasional fits of hunger amounting to bulimia, at other times there may be great thirst, the so-called nervous diarrhea may also occur. Associated with these symptoms are epileptoid convulsions, chorea, headaches, neuralgia and angina pectoris. In these atypical cases flushings, which the patient calls rushings of blood to the head, excessive sweating, and subjective temperature are of diagnostic value. The patient often complains of a difficulty in swallowing. A dirty, yellowish pigmentation of the skin is often present, being a lighter shade than the bronzing of Addison's disease. I have seen a case where the tremors, the nervousness and the discoloration of the skin in patches around the eyes, the nipples and on the back of the hands, with slight convulsions, were the main symptoms. There are also usually irregularities of the menstrual function. In males loss of sexual desire and impotence are common causes of complaint.

The hair falls out in a considerable number of cases.

The urinary derangements are polyuria, albuminuria

and glycosuria. Diacetic acid may be present where vomiting is severe, owing to starvation. The nitrogen elimination is increased at least in the earlier stages, being markedly more than the amount taken in the food.

Of the cardinal symptoms of Basedow's disease the exophthalmos is usually absent or very slight and the enlargement of the thyroid may not be palpable.



FIG. 76.



FIG. 77.

Masked Basedow's disease with slight exophthalmos.

The blood pressure is usually normal but there is not the rise either in mean or maximum pressure which should occur on taking the erect position; for example, in a case in which the diagnosis of atypical Basedow's disease was made the blood pressures were:

Reclining.—Pulse 95, mean p. 101, maximum p. 140 = 0.726.

Standing.—Pulse 105, mean p. 95, maximum p. 135 = 0.703, showing that the vasomotor system was abnormal.

The diagnosis of these cases has usually to be made by exclusion, but the abnormal postural variations in the

blood pressure, the sweatings, flushings, rapid pulse, discoloration of the skin, fine tremors and nervous irritability are usually sufficiently marked to enable the physician to make a diagnosis.

*Treatment.*—The medicinal treatment of Basedow's disease has not so far proved very satisfactory, and the opinion of today is in favor of surgical interference. Many cases can, however, be improved and even cured by careful attention to details and by the intelligent use of drugs.

All cases of peripheral irritation should be removed as far as possible and excitement of any kind avoided, the patient leading a quiet routine life, in which nothing should be attempted likely to increase the rapidity of the heart's action. When the case is severe the patient should remain in bed. The diet should be plain and nutritious, stimulants, such as tea, coffee, alcohol or tobacco, should be forbidden or reduced to a minimum. It is not wise in this or any other disease to absolutely interdict habits which are perhaps lifelong. The worry of the unsatisfied desire for the stimulants is usually worse for the patient than their moderate use.

The dietetic treatment is strongly advocated by Thomson on the etiologic theory of a toxemia. It consists of a milk diet, preferably using fermented milks, such as Koumys, Matzoon, Zoolak, etc. Poultry, fish, oysters and eggs with well baked or perfectly toasted bread are to be used in moderation; vegetables, such as asparagus, tomatoes, beets, turnips, carrots, spinach, peas and beans, are prohibited, as well as red meats; any food which is tasted in eructations is to be avoided, a good rule to follow in all dietetics. Thomson's medicinal treatment consists principally of intestinal antiseptics, mercury being preferred in the form of blue mass pill once or twice a week. I have found that one-thirtieth gr. of the bichlorid combined with five grs. sodium glycocholate-mass three times a day after

meals is more effective; almost invariably it reduces the pulse rate, at the same time stimulating the liver. For the gastric disturbances he employs resorcin, bichromate of potash, bismuth, salol, etc.

Other drugs, arsenic, quinin, strychnin, digitalis, iron, ergot, are all described as being indicated and producing amelioration of the symptoms. Probably strophanthus and belladonna are the most reliable of the empiric treatments. On the theory that the secretion of the thyroid was chemically altered and that therefore there was a hypothyroidea, desiccated thyroid and thyroidin have been administered with apparent success in a few instances, but most observers report, as would be expected, that the symptoms were either not affected or were aggravated under the treatment. Orthophosphate of soda or potash, the latter is to be preferred, as it is less likely to produce diarrhea, or better still, phosphoric acid in full doses, have produced marked benefit in many cases, being especially advocated by Professor Kocher of Berne. There is some connection between the phosphorus metabolism and the thyroid secretion. Administration of phosphorus seems to restore the balance of the iodine in organic combination in the colloid substance, decreasing it when too high and increasing it when too low.

As the physiological action of the suprarenal gland is diametrically opposed to that of the thyroid it occurred to the writer that it ought to at least relieve the symptoms due to the hyperthyroidea, further it had been shown that when the thyroidin molecule is saturated with iodine it becomes inert. On these principles desiccated suprarenal and Lugol's solution were administered in a very marked case in 1898 with complete success; in 1899 Dr. Todd treated a case in the same manner with success, since which date Dr. E. L. Whitney and others have tried the treatment in several cases and the majority have done well.



Occasionally the addition of a little strychnia has materially assisted the heart symptoms. This treatment seems to give the best results in those cases which occur at puberty, menstruation or during and after pregnancy, and in the atypical cases referred to above phosphoric acid combined with this treatment has also apparently been of use.

Electricity has been strongly advocated by M. Vigroux and others. He recommends that the constant current should be applied to the neck and the interrupted current to the precordial region. In using the constant current the electrodes should be firmly pressed deep into the neck beneath the angle of the jaw at each side for about seven minutes or until the skin is slightly red. The strength of the Faradic current depends upon the sensations of the patient, bearing in mind that they are in a nervous and excitable condition.

In the most severe cases medical treatment fails and recourse has to be made to the surgeon. Ligation of the thyroid arteries and partial removal of the gland is attended with considerable success, the mortality being about 1 per cent or less. In cases where the exophthalmos is the most severe symptom, section of the cervical sympathetic is said to be followed by good results.

Some observers have claimed that thymus feeding has produced good results in some cases. It seems hardly probable, however, that feeding with a gland which should have atrophied under normal conditions and which is pathologically persistent in the majority of severe cases should produce any good effects.

Recently attempts have been made to treat Basedow's disease by means of a serum but with only very partial success. Portis endeavored to produce symptoms similar to those which follow removal of the thyroid and parathyroid glands in animals by means of specific cytotoxins

whose action was selective on the thyroid and parathyroid cells, producing degeneration and loss of function. Man-kovsky and Goutscharukov claim they have made a thyro-toxic serum which produced symptoms resembling tetany, the thyroid cells showing evidence of degeneration. Man-kovsky introduced the thyroid glands of dogs into the peritoneal cavity of cats at fourteen day intervals; after the third injection the serum was separated and proved toxic to dogs. Goutscharukov used the thyroids of dogs, injecting them into rams, producing a serum which was thyro-toxic. Portis employed emulsions of dogs' thyroids; beginning with one gland he increased the dose to ten glands which he injected into the peritoneal cavity of a goat. He claimed that the serum of the injected animal acquired certain characteristics. Injected into dogs it produced depression, convulsions, vomiting, rapid breathing, hemoglobinuria and death; in other cases fever, lachrymation, emaciation and progressive loss of weight. The thyroid showed absence of colloid substances, desquamation and disintegration of the epithelial cells, followed by the development of papillary proliferations; there were degenerative changes in other organs. Moebius, assuming that the blood of thyroidectomized animals would contain certain bodies which would normally have been destroyed by the thyroid secretion, considered that they might be used to neutralize the excess of thyroid secretion in Basedow's disease. Lanz employed the milk from thyroidectomized goats in several cases with good results. Moebius serum was prepared by Merck and used with satisfactory results by J. Moebius and Schultes, but Murray was unable to obtain any results.

Dr. Murray of Newcastle-upon-Tyne prepared a serum by feeding rabbits on gradually increasing doses of thyroid extract, but obtained no definite results. Lepine prepared

#### THE THYROID AND PARATHYROID GLANDS.

a serum in a similar way by feeding a goat on sheep thyroids.

One or two cases have been reported where parathyroid feeding produced good results, but further experiments are necessary before definite conclusions can be reached on this point.

## CHAPTER XIV.

### THYROID FEEDING IN GENERAL THERAPEUTICS.

The thyroid has an especial therapeutic action which can be utilized to advantage even when there is no deficiency in the secretion of the gland of the patient. As shown in a previous chapter, its administration dilates the arteries, reducing the blood pressure, thereby accelerating the heart's action and decreasing the work of that organ; it also increases metabolism, causing an increased elimination of nitrogen as well as of carbon dioxide; it also acts as a diaphoretic by dilatation of the vessels of the skin; is a slight diuretic and increases the oxygen-carrying power of the blood. Probably its primary actions are the dilatation of the vessels and the increased oxidation.

The use of thyroid as an accessory to other treatments is perfectly rational, especially in cases where there is high arterial tension with increased mean pressure: the vasodilators of the Pharmacopeia are too fugitive in their action to be of much value except in emergency, but in the thyroid we have a drug which can be administered for any length of time and which is the natural drug, so to speak, of the body.

One point in the physiological action of thyroid and in which it acts differently to the nitrates is its effect on the capillary circulation. The nitrates appear to dilate the arterioles, thereby increasing the heart rate, but they do not produce an increased bulk of blood in the peripheral circulation. The administration of thyroid appears to dilate the capillaries at least of the skin, producing marked reddening and diaphoresis; this point is further emphasized by the dry harsh condition of the skin in hypothy-

roidea. The thyroid is the only drug in the writer's experience which acts as a capillary dilator; the Nauheim baths have the same effect, with this advantage, that at the same time the pulse rate goes down.

When the first successes were recorded thyroid was utilized in almost every kind of disease without any attention being paid to its indications and limitations; it appeared as if the dream of a universal medicine was about to be realized. The medical literature of the nineties abounds in reports of its successful use in albuminuria, epilepsy, diseases of the skin, gout, tuberculosis, the fevers, leprosy, etc., but whatever good effects were obtained were due either to the cases being atypical myxedema or to the beneficial effects of its physiological action, as stated above, upon the patient.

#### OBESITY.

There is a form of obesity which seems to be due to a loss of function of the thyroid gland and which shows but few symptoms of myxedema. They are generally cases where there has been a somewhat sudden increase of adipose deposit over the whole body following some acute disease, such as typhoid fever, or in women after pregnancy, or when the climacteric has arrived at 35 or 40 years of age. These patients will usually complain of rheumatic pains in the limbs, which they ascribe to the extra amount of weight they have to carry. There are also often nervous disturbances which may be due to fatty heart, consisting of giddiness and faintness combined with a nervous condition which simulates hysteria. Nervous attacks of this nature occur at irregular intervals without any apparent cause, the patient may be domineering and irritable, causing family troubles. There are few physical signs except the obesity which may be confined to the face and body, the lower limbs being but little larger than normal.

There is a peculiar change in the contour of the neck, which appears square, the anterior central portion failing to project. Occasionally the symptoms of myxedema may be present in an attenuated form, at other times they are entirely absent.

In these cases great care should be exercised in the administration of the thyroid; on no account should more than one grain per day be given at the commencement, increasing the quantity very slowly and keeping the patient under close observation. It is well to give a little arsenious acid and strychnia or *adonis vernalis* at the same time. Very serious accidents may occur from an overdose of the thyroid in these cases, owing to the condition of the heart and the anemia of bulk which exists in the obese. It has been shown that in the moderately obese the total weight of blood in circulation may be as low as one-thirty-third of the body weight, when it is obvious that any dilatation of the vessels may produce very serious collapse. Constipation is often a very troublesome accompaniment of obesity, but if the disease is due to thyroid insufficiency the first sign that the thyroid treatment is indicated will be the regulation of the bowels.

Thyroid feeding is not an "antifat" of universal application and should always be given with caution. It is true that if large enough doses are given any patient will lose flesh, but the heart failure and depression of spirits resulting prevent its use.

## GLYCOSURIA.

The increased metabolism of carbohydrates and fats produced by the administration of thyroid naturally suggested its use in glycosuria. At the suggestion of Dr. E. L. Whitney it was administered to several patients who had sugar in their urine, and where possible, prescribing a mild diabetic diet, viz: the patient to abstain from all

starchy foods and sugars, substituting as much fat, in the shape of oil, butter, cream, fat meat, etc., as possible, but allowing one slice of toasted bread twice or three times a day. It is an easy matter to prescribe a diet but a very difficult thing to get a patient to keep to it, but it was found that by allowing this small amount of bread the patient was able to keep to the diet without much discomfort. There are probably several forms of glycosuria, nervous, muscular, hepatic, pancreatic and possibly renal. The thyroid treatment could presumably only be indicated in the hepatic and muscular forms, while general improvement of the metabolism might be successful in the nervous form. In the pancreatic form, although I have never tried it, I should consider it as contraindicated.

In cases of glycosuria occurring in old age, obesity, as well as in some of those occurring in middle life, the above diet, coupled with the administration of two grains of desiccated thyroid and five grains of sodium glycocholate-mass (Hynson & Westcott, Baltimore), to increase the absorption of fat and to purge the liver, have brought about complete recovery in several cases, so that on returning to their ordinary diet there was no return of the glycosuria. In other cases in which the diagnosis of hepatic glycosuria was made the treatment failed, though in most cases there was an improvement in the general condition of the patient which was probably due more to the diet than to the drugs.

#### SENILISM.

In old age the thyroid atrophies under normal conditions and although the administration of thyroid will not restore youth, it will, if given in small doses with some stimulant, such as opium or strychnin and arsenious acid, improve the action of the heart and dilate the vessels, increasing the bulk of the circulation to the various organs. In senilism it must be administered with caution, as

atheroma of the arteries or fatty degeneration of the heart muscle may exist.

#### BRIGHT'S DISEASE.

In the early stages of this disease, when the headaches, the dizziness and the dilatation of the left ventricle have commenced, all of which symptoms are primarily due to increased mean blood pressure, thyroid will often relieve the symptoms and arrest the disease in its progress. The highest mean blood pressure the writer ever found, 215 mm. Hg., was in a man of 59 years of age, who complained of the most agonizing paroxysms of pains in the head and limbs and who had an apex beat to the left of the nipple, a slight trace of albumin in his urine with other symptoms of early Bright's. He was relieved by thyroid treatment and up to the present the disease does not appear to have progressed. Many cases can be relieved and the progress of the disease arrested by using the thyroid as a means of reducing the blood pressure and attending to the digestive organs and the intestinal tract.

#### EPILEPSY.

It would seem that thyroid treatment would be indicated in epilepsy, as the contraction of the vessels is the immediate cause of the spasm, but experience has shown that not only does the treatment do no good but is positively harmful, increasing the number and severity of the spasms. There have been a few cases recorded where the administration of thyroid appears to have relieved and even cured but they are rare. Parathyroid feeding would be presumably indicated from the results of the physiological experiments detailed in a previous chapter, and Dr. Charles G. Hill gave thyroid and parathyroid to an idiotic epileptic child in Mount Hope Retreat. The child improved in mentality and grew considerably, he also became clean in his habits, his seizures were less frequent



and much less severe, but whether this latter was due to the parathyroids or to his general improvement it is difficult to say. In another case of epilepsy in a young man the parathyroids were given alone with very great improvement, the seizures being reduced from one or two a week to one or two in three months. In a third case Dr. Hill reports decided improvement. These results are sufficiently satisfactory to call for a further trial of the drug.

#### MENSTRUAL DISTURBANCES.

From the connection of the thyroid with the organs of generation it is in this field that the most beneficial results should be expected; probably no drug is of so universal a benefit in menstrual disorders as the thyroid. At puberty, when menstruation is delayed, irregular or scanty, a small dose of thyroid daily for a month or two will often bring about a normal menstruation with improvement of the general health. In young women who suffer from amenorrhea or dysmenorrhea the same treatment is usually effective and should always be tried before the patient is condemned to a surgical operation. It should be remembered, in examining these cases, that many of the acute diseases of childhood produce a sclerosis and consequent loss of function of the thyroid gland, which may render it incapable of developing sufficiently at puberty for the increased call upon its functionation. The thyroid, as was stated in the chapter on Physiology, increases in size prior to puberty and enlarges at every menstruation as well as during pregnancy, and it is therefore evident that its functionation acts as a stimulating cause to the sexual processes. In cases of grown women, and especially those who have not been married, it often happens, though no atrophy of the gland can be detected, that the stimulus of an extra amount of thyroid secretion given as desiccated thyroid will reestablish menstruation. At the climacteric,

especially when occurring prematurely, the drug is often of benefit, sometimes reëstablishing menstruation for a time and relieving the various minor symptoms which are so common at this period.

Dr. Charles G. Hill, of Mount Hope Retreat, was the first to observe this very important result of thyroid feeding. He noticed that in some of the chronic insane who had not menstruated for a year or two there was a return of the flow after one or two months' treatment, invariably causing improvement in their physical and mental condition. For some reason, which is at present inexplicable, the administration of parotid gland is said to have a beneficial effect upon some cases of dysmenorrhea and is at times combined with thyroid treatment. It must be remembered that unlike other emmenagogues which can be administered in large doses, producing their effects in a day or two, thyroid must be given daily for a month, doubling the dose for a day or two before menstruation is due, and it may take two or more months before the end is attained. In many cases which had been diagnosed as retroflexion of the uterus by gynecologists and upon whom they had operated without giving relief, a course of thyroid treatment has brought about normal functionation and perfect health.

#### TETANY.

Tetany is produced by thyroidectomy and occasionally occurs as a symptom in cachexia strumipriva, showing that it can be produced by cessation of function of the thyroid and parathyroid glands; certain experiments detailed in a previous chapter seem to point to the latter being the etiologic factor. In those cases of cachexia strumipriva which survive the tetanic symptoms may disappear for a shorter or longer period, reappearing during pregnancy or some other excitant.

Tetany is usually associated with disturbances of the

digestive tract and is probably due to a toxemia; it has also been known to occur as an epidemic. Emotions, muscular effort, dentition and rachitis are all given as exciting causes. It occasionally occurs in Basedow's disease. Infancy, puberty, menstruation, lactation and pregnancy are the periods at which it most commonly occurs. The disease has been recorded as associated with gout, rheumatism and malaria.

There are certain forms of epilepsy which have been described as "tetanoid epilepsy," in which there are only tonic contractions. The head may be turned, the arms extended, elbow joints flexed and fingers flexed, the latter in the interosseal position. The spasm may last for a longer or shorter time, the muscles affected varying, there may be frothing at the mouth and the tongue may be bitten, the distinctive point being that there are no clonic convulsions as in the true epileptic seizure.

In certain cases in childhood the tetany may be due to defective thyroid secretion, cases being on record where thyroid treatment has proved effective. The physician often never sees the patient during the seizure and has to be content with the report of the friends as to the nature of the convulsions. Consequently he is unable to make the distinction between a tetanoid and a true epileptic seizure. Though by far the greater number of convulsions in childhood are due to digestive disturbances, it is a point worthy of careful investigation, especially if the attacks occur at intervals, as to whether the attacks are epileptic or tetanic in their nature and in the latter case to examine for possible hypothyroidism.

The importance of the thyroid during menstruation, pregnancy and lactation has been emphasized in preceding chapters, and convulsions occurring at these periods without any apparent cause point to thyroid insufficiency. Attacks occurring during pregnancy, labor or lactation

are usually termed eclamptic. Recent investigations go to prove that eclampsia is due to thyroid insufficiency in a certain number of cases. There are cases where convulsions occur during the latter months of pregnancy as well as during labor, which continue at intervals without these exciting causes.

A case occurred in the writer's practice where a married woman had had convulsions during pregnancy and labor on three occasions, giving birth to healthy children. During the fourth pregnancy and labor no convulsions occurred; with the fifth and last pregnancy there were again convulsions. On recovery the seizures returned at intervals, sometimes as often as two or three times per week. The convulsion consisted in tonic contractions only, the patient being partially conscious during the attack. She was treated with large doses of thyroid, as high as 30 grs. per diem; the seizures were reduced in number and severity but after treatment was suspended they gradually increased in number and severity, again decreasing on the resumption of treatment.

From experimental and clinical evidence it is probable that a certain number of cases of tetany which simulate epilepsy are due to thyroid insufficiency.

## ECLAMPSIA.

The consensus of opinion at present is that eclamptic convulsions are the result of an autointoxication, and that the conditions existing are an increased mean blood pressure, a perverted metabolism, a decreased elimination by the kidneys, with, in the majority of cases, albuminuria with or without casts, the pathologic findings being fatty degeneration of the liver and kidneys. The placenta may be looked upon as a digestive organ preparing the nutrition for the fetus, and possibly it may also have a hepatic function destroying the toxic products of fetal metabolism

before the fetal blood enters the vena cava; consequently a pathologic condition of the placenta might produce toxemia in the mother.

The connection of the thyroid gland with the organs of generation has been well established, the gland enlarging at puberty and during menstruation, pregnancy and lactation. The far-reaching effect of hyposecretion of the gland and the various disturbances the condition produces has led many investigators to experiment as to the possibility of producing eclampsia by partial thyroidectomy.

In experimenting with thyroidectomy Halstead observed that a bitch, who had been deprived of a large portion of her thyroid gland but remained in apparently perfect health, became impregnated by a normal dog and progressed without any signs of hypothyroidism till term, but at delivery showed all the symptoms of athyroidism, including convulsions. Since this observation many experiments have been made on this point, notably those of Verstraeter and Vanderlinden (*Ann. de la Soc. de Med. de Gand.*, 1897), v. Eiselberg (*Die Krankheiten der Schilddrüse*), I. Jeandelize (*Insuffisance thyroïdienne et parathyroïdienne*) and Lange (*Zeit. f. Geburt. u. Gyn.*).

The latter removed one-fifth of the thyroid gland from 10 pregnant cats; 2 died in coma, one 23 days and the other 38 days after the operation, 3 had convulsions 23 and 25 days after operation. Three of these cases had albuminuria and at autopsy fatty degeneration of the liver and kidneys was found. The other five cats remained well, but at autopsy three of them were found to have the same pathologic lesions. Lange also examined a series of 133 cases of pregnancy and found that the hypertrophy of the thyroid commenced in the fifth month in multiparas and in the sixth month in primiparas; he also found on the administration of small doses of thyroid to pregnant women with enlarged thyroids that the gland returned to

normal size, but on the cessation of the treatment it again hypertrophied. Of the 133 cases examined he found the gland enlarged in 108 cases, 3 were doubtful, in 22 there was no enlargement, of the 22 twenty showed albuminuria, 16 albuminuria with casts, 6 of these cases developed eclampsia; of the 108 with hypertrophied gland only two had albuminuria and one of these was a nephritic; none of the 108 developed eclampsia.

Herrgott reports a case of incomplete myxedema where eclampsia developed. Verstraeter, Vanderlinden and Nicholson (*The Scot. Med. and Surg. Jour.*, 1901) report cases of eclampsia, which they attribute to thyroid insufficiency, the latter treating a case with thyroid with success.

The thyroid function being increased during pregnancy it is evident that if for any reason the thyroid has failed to fully develop, though secreting sufficient under ordinary conditions, it will fail to respond to the excessive demand upon it during pregnancy. It is by no means uncommon for the thyroid to be affected by the acute diseases of childhood, rheumatism, typhoid, etc., as has been shown by Garnier and Roger; consequently at the first pregnancy there is a deficiency of thyroid secretion which may be a factor in producing eclamptic convulsions at term in primiparas. The excitation of the gland during pregnancy will have a tendency to increase its functionation, preventing the recurrence of the symptoms at the next pregnancy. In other cases the gland never acquires a sufficient secreting power and eclamptic convulsions occur at every successive labor. In those who have no eclamptic symptoms at the first pregnancy, but in whom they appear in the later pregnancies, it may be assumed that the strain upon the gland during the first pregnancy or some intercurrent disease has affected the functionation of the gland.

The principal symptoms of eclampsia are the same as

those of hypothyroidea, viz: high mean arterial pressure, decreased elimination by the kidneys, perverted metabolism and very often albumin and casts. In partially thyroidectomized animals the same symptoms occur while the principal pathologic lesion is fatty degeneration of the liver and kidneys. From the above data it is probable that a certain number of cases of eclampsia are due to a hyposecretion of the thyroid and parathyroid glands.

The following case occurred in the practice of Dr. Charles G. Hill:

A primipara was examined six weeks before term. Her 24 hours' urine was found to contain 11.37 grms. albumin, with some casts, the nitrogen occurring as urea, 79.8 per cent; ammonia N, 9.2 per cent; uric acid N, 1.8 per cent; residual, 9.2 per cent; chlorids, 10.4; phosphoric acid,  $P_2O_5$ , 2.65:

$$\frac{\text{carbon } 0.16}{\text{nitrogen } 7.98} = 0.77.$$

The blood pressure showed a very high mean in proportion to the maximum

$$\frac{\text{mean } 168 \text{ mm. Hg.}}{\text{max. } 208 \text{ mm. Hg.}} = 0.8,$$

with a pulse of 105. Dr. Hill, who had attended her before marriage, had diagnosed hypothyroidea when she had improved under thyroid treatment. He gave her full doses of thyroid and parathyroid, the blood pressure falling under the treatment to

$$\frac{\text{mean } 152 \text{ mm. Hg.}}{\text{max. } 198 \text{ mm. Hg.}} = 0.76;$$

pulse, 95; the relation of maximum pressure to mean pressure being nearly normal. She was delivered two weeks before term without any accident. The day after delivery the blood pressures were

$$\frac{\text{mean } 140 \text{ mm. Hg.}}{\text{max. } 182 \text{ mm. Hg.}} = 0.7$$

or normal. Nineteen days after delivery albumin was absent from the urine; urea N, 83.7 per cent; ammonia N, 8.0 per cent; uric acid N, 0.55 per cent; residual N, 7.75 per cent, being normal except for the still high proportion of ammonia N:

$$\frac{\text{carbon } 4.56}{\text{nitrogen } 4.48} = 1.0;$$

chlorid, 6.4; phosphoric acid,  $P_2O_5$ , 1.68. The thyroid treatment was discontinued at the time of delivery, but commenced again on the fourth day, as the urine became scanty, the pulse hard and lactation had not commenced. In a day or two the lactation was normal, the patient making an uninterrupted recovery.

## IMPOTENCE.

Impotence in man and frigidity in woman are conditions which are occasionally benefited by thyroid treatment. In man when the want of sexual power is due to a non-development of the penis, as shown by the small size of the organ with an elongated prepuce covering the glans which is with difficulty withdrawn, and when the testicles are small and soft to the touch, the scrotum without the pigmentation and the rugæ of the normal adult, combined with a history of congenital want of power and possibly also of desire, a course of thyroid feeding, extending over several months, will sometimes produce a marked development of the penis, the prepuce withdrawing from the glans, the testicles enlarging and becoming firm to the touch and the scrotum normal in appearance. The desire and capability for the sexual act may become normal and even excessive. I have often observed among the insane that patients under thyroid treatment became intensely erotic,



masturbating continually. This is more often observed in females. Occasionally the treatment had to be suspended owing to the sexual excitement it produced. If the impotence is due to pollutions or spermatorrhea or any derangement of the circulation of the organs, thyroid treatment is, of course, useless, but in those cases where there is no apparent cause and especially when the patient is obese the treatment is often successful. In the female it is difficult to diagnose arrested development of the sexual organs, but should there be a history of delayed menstruation with a tendency to masculinism the treatment will often increase the sexual desire.

In cryptorchidia, either unilateral or bilateral, thyroid feeding will sometimes cause the descent of the testes.

It is obvious that this treatment is only indicated in isolated cases where there is evidence of arrested development of the organs or loss of thyroid function. A female patient, who was under thyroid treatment for amenorrhea and delusions, complained of almost uncontrollable sexual desire after the menstruation had been established and the delusions had disappeared.

From the connection of the thyroid with the sexual organs, its increase in size at puberty, during menstruation and pregnancy, as well as from the fact that in cretinism and infantilism the genitalia do not develop and puberty is either never established or delayed for it may be years, it is surprising that more cases of impotence in the male and frigidity in the female are not benefited by thyroid treatment.

#### NERVOUS DISEASES.

As has already been stated the action of the thyroid is alterative. By dilating the vessels it brings an increased blood supply to the organs and tissues of the body and consequently may and does act beneficially in many dis-

eases. In most cases where there is an increased mean blood pressure thyroid medication will do good, provided it is not pushed so far as to produce thyroidismus or mental depression from its effect upon the heart. In some of these unclassified conditions which are grouped in the conglomeration of "functional neuroses" it will be found on careful examination that there are symptoms of incomplete or marked myxedema, while in others the increased mean pressure is an indication for thyroid treatment.

#### PARALYSIS AGITANS—PARKINSON'S DISEASE.

This disease is ascribed to exogenous toxemia from alcohol, lead, mercury, etc., but variability and the absence of nerve lesions seems to point to some constitutional defect or to autotoxemia. Castelloi considers that autointoxication is the etiologic factor. The tremblings, sensations of heat and other symptoms common in this disease also occur in exophthalmic goitre, which led him to think that the thyroid might be implicated. In two post-mortems he found in the first that the thyroid only weighed 145 grains and in the second the gland was cystic. He also claims to have had good results from thyroid feeding.

#### DISEASES OF THE SKIN.

Thyroid treatment has been found to be of benefit in many cases of skin disease, notably psoriasis, due no doubt to the increased circulation in the skin. It will be remembered that one of the most marked symptoms of myxedema is connected with the skin, the pseudoedema and the dry, scaly, harsh condition, with the absence of perspiration and secretion of the sebaceous glands show that the circulation is decreased. It is probable that the benefit derived in skin diseases from thyroid treatment is due to the increased circulation to the parts.

## ADIPOSIS DOLOROSA.

Of this rare disease only five cases have yet come to autopsy, four having been reported by Dr. F. X. Dercum and one by Dr. Burr. In two, gross disease of the thyroid was found, the glands being the seat of calcareous deposit; in the third there was irregular atrophy of the thyroid gland with efforts at compensatory hypertrophy; in the fourth there were the same changes in the thyroid with enlargement and gliomatous degeneration of the pituitary body. In the fifth case the changes in the thyroid were slight, but there was adenocarcinoma of the protuberance of the pituitary body and hemolymph glands. The relation of the thyroid to this disease seems to be established, but is probably combined with diseases of the pituitary body. Thyroid treatment does not seem to have ameliorated the symptoms.

In akromegaly there seems to be some derangement of the thyroid gland, but up to the present the etiology of the disease is unknown.

## HEMORRHAGE.

In certain cases of persistent hemorrhage the administration of thyroid extract in 5 gr. doses with the addition of calcium chlorid will increase the coagulative power of the blood. Dr. Bloodgood reports cases where he found this treatment effective when other methods of arresting bleeding had failed.

## MENTAL DISEASES.

The use of the thyroid in insanity dates from 1892, when it was used in the Morningside Asylum in Edinburgh with very good results, since which time it has been used with varying success by different specialists. There has been unfortunately an idea prevalent that the treatment was applicable to all forms of insanity and it has

been used without discrimination, no attention being paid to the symptomatic indications for its use. Several specialists have given it to a large number of cases and, reporting improvement or cure in about 5 per cent of the cases, were disappointed at the result. Easterbrook finds it of benefit in about 9 per cent of all cases, but disease of the thyroid gland is said to be more prevalent in Scotland than in this country. In the experience gained at Mount Hope Retreat I am of opinion that about 5 per cent of all cases are improved by the drug and in many of these it is only as an accessory to other treatment that it is of benefit.

The number of insane patients suffering from myxedema, even in an atypical form, is probably very small and, as the mental disturbances may assume the form of dementia, melancholia, or mania, the psychic disturbances are no guide to the therapeutic use of thyroid. It is very rare that it is of any use in the acute stages of the disease and has the objection of decreasing the appetite, sometimes producing absolute refusal of food, and further a drug which increases metabolism and elimination of both nitrogen and carbon must be contraindicated when there is poor assimilation and the system run down. Before commencing to administer thyroid the digestive organs should be got into a healthy condition and it is a good rule not to give thyroid unless the nitrogen elimination is at least 8 to 10 grms. in the 24 hours. In cases of true myxedema this does not apply, as often in these cases the nitrogen is as low as 5 grms. and rises, the appetite improving at the same time on the administration of thyroid.

The indications for thyroid treatment are the same in insanity as in other diseases, the condition of the circulation being the principal guide. In cases of acute mania, where the mean and maximum blood pressure are low, the heart action weak and the patient suffering from anemia of bulk, it is strongly contraindicated and may produce

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serious results. On the other hand, in cases where the pulse is full, strong and rapid, the mean and maximum pressure high, the nitrogen elimination 15 grms. or even more, with a good appetite and hyperchlorhydria of the stomach, thyroid combined with opium will often produce very good results, the thyroid counteracting the contraction of the abdominal vessels and heart stimulation of the opium.

When there is marked venous stasis, pointing to insufficiency of the right heart, and where the mean pressure is normal or little above normal, and the maximum pressure low, thyroid is contraindicated, as it will increase the amount of blood on the venous side of the circulation by dilating the arterioles; on the contrary, if there is a dilatation of the left side of the heart, with high mean pressure and either normal or low maximum pressure, digitalis, strychnin or adonis vernalis should be added to thyroid feeding. In melancholia, when the mean blood pressure is often very high, thyroid is a valuable accessory to the opium treatment.

When the acute stage of the disease is past, the digestion and appetite improved and the elimination sufficient, thyroid in small doses is very useful, increasing the amount of the circulation and consequently the nutrition of the organs, patients often gaining weight during its use.

Puerperal insanity is probably the most uniformly benefited, the reason being that the thyroid has suffered from hypersecretion during pregnancy and is suffering from cell fatigue, but hypothyroidea is certainly not the cause of puerperal insanity or at least only in very rare cases.

It would seem probable that the thyroid would act as an hypnotic from its action upon the blood vessels, reducing the bulk of blood passing through the brain; in the ordinary sense, viz: that a dose at bedtime will produce sleep, it certainly is neither a hypnotic nor an anodyne,

but often the addition of a small dose of thyroid to the daily medicine will in a few days render the use of a hypnotic unnecessary. Here again the indications for its use must be looked for.

There are some cases of delusional insanity which seem to be entirely due to thyroid insufficiency; for example, a young woman of about 28 years of age, in the practice of Dr. MacCalman, complained of visions of "seeing the dead" at night. This delusion occurred once or twice a month and was so vivid that she would scream and run to another room for protection, leaving her in a very nervous condition. She could give no very clear account of any disease before puberty, but stated that she had not menstruated until her twentieth year, having had scanty and at times painful periods all her life. Her hair fell out at irregular intervals, her mean pressure was high; her thyroid gland could be palpated and was evidently enlarged, feeling hard to the touch. On these symptoms she was prescribed thyroid. During the first month of treatment she had one vision, her menstruation was free and normal and she had no more visions for some time while taking six grains a day. She stopped the treatment and the visions returned, disappearing again on resuming treatment.

In the administration of thyroid there are several points which are of great importance: the initial dose should nearly always be small, one grain three times a day is, as a rule, safe and can be gradually increased, but it is very rarely necessary to go above two grains. Another point is the condition of the digestive tract, as thyroglobulin is precipitated by organic and inorganic acids, it is important that alkalis should be administered at the same time, as should the intestines contain large quantities of organic acids, a by no means uncommon condition, the drug will be only partially absorbed. The condition of the heart

requires watching, as an overdose may produce serious results and very great depression of spirits; especial care is required in old people where atheromatous arteries and fatty heart may exist. Of the drugs which are advantageously combined with the thyroid arsenious acid is generally indicated and appears to aid the treatment. Strychnia, digitalis and adonis vernalis, especially the latter, are of benefit when the heart is weak and the dilatation marked. Opium in nervous diseases gives better results in many cases when combined with thyroid, the latter counteracting the tendency of the opium to contract the arterioles.

Thyroid treatment is no universal panacea for every ill that flesh is heir to, but bearing in mind its physiologic action and seeking for the indications for its use it is undoubtedly a valuable therapeutic aid.

#### THE THYROID DURING FETAL LIFE.

In the sixth week of intrauterine life the organs of the thorax and upper part of the abdomen may be said to have completed their development; that is to say, they grow during the remaining 34 weeks but show no changes in construction till birth forces new functions upon them. At this period the development of the thymus from the entoderm of the third gill cleft has begun, the two lateral anlages of the thyroid unite with the single median anlage at the seventh week, the ductus thyroglossus may remain open till the eighth week while hollow acini have commenced to form.

At birth the isthmus of the thyroid gland lies in front of the trachea, opposite the body of the fifth and sixth vertebræ; with the head flexed it is in contact with the upper border of thymus, its lateral lobes extending from the lower border of the thyroid cartilage to the level of the fourth or fifth tracheal ring. The weight of the gland is

given by Ballentyne as 7 grms. The writer has found the average weight in two stillborn children at term to be only 1.4 grms.; other writers place the average weight at about 2 grms.

The thyroid is known to be the great regulator of body metabolism and to be essential for growth; in at any rate the early years of life defects in it are the cause of cretinism and infantilism, diminished thyroid activity leading to a decrease of the nutritive processes. The thyroid function is increased during pregnancy and also during lactation, the marked flow of milk on the third day of the puerperium is due to the increase of the thyroid secretion in the maternal blood caused by the birth of the fetus. Experimentally it has been shown as stated in a previous chapter, that the administration of thyroid increases the secretion of milk. The question arises, Has the thyroid of the fetus the same regulating function in connection with the metabolism of antenatal life as the thyroid of the mother over adult life, or has the thyroid of the mother the double function of regulating both the maternal and the fetal metabolic processes? It has been shown by experiment, as stated in a previous chapter, that if the thyroid of the mother be removed there is apparently a compensating hypertrophy of the thyroid of the fetus; it has further been shown that the fetal thyroid contains no iodine and in a number of cases that I have examined of stillborn children at term and also of children who have lived a few weeks that there is no iodine in the gland. The fetal gland contains thyromucin, but it does not contain the substance which quickens the pulse and lowers the blood pressure. Whatever may be the function of the fetal thyroid during fetal life it is evident that it is from the maternal gland that the fetus receives the active principle, and further that as the child at birth and for some time after has no thyroxine in the thyroid it must

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receive the amount which it requires from the mother through the milk. In the cow it is otherwise; the gland of the fetal calf contains iodine as well as the substance which increases the pulse rate and reduces the blood pressure. It seems probable that under these circumstances that cow's milk will not contain any thyroxine while human milk will contain it.

It seems possible that the difficulty of rearing infants on artificial food may be due to the absence of thyroxine in the cow's milk.

Quantitative analyses of the thyroids for iodine and thyroglobulin were made of six children dying of inanition. In no case was any iodine found in the gland and the amount of thyroglobulin estimated by Oswald's method gave the following results:

| CHILDREN DYING OF INANITION.  |                             |               | NORMAL CHILDREN.              |                             |               |
|-------------------------------|-----------------------------|---------------|-------------------------------|-----------------------------|---------------|
| <i>Weight of<br/>Thyroid.</i> | <i>Thyroglob-<br/>ulin.</i> | <i>Iodin.</i> | <i>Weight of<br/>Thyroid.</i> | <i>Thyroglob-<br/>ulin.</i> | <i>Iodin.</i> |
| 1.4                           | 0.0912                      | absent        | 1.9                           | 0.4686                      | trace         |
| 1.4                           | 0.0882                      | "             |                               | (2 yrs. old)                |               |
| 0.64                          | 0.0574                      | "             | 1.3                           | 0.1083                      | absent        |
| 0.9                           | 0.084                       | "             |                               | (stillborn)                 |               |
| 1.45                          | 0.089                       | "             | 1.4                           | 0.1029                      | "             |
| 0.7                           | 0.035                       | "             |                               | (stillborn)                 |               |

The above analyses show that in children dying of inanition the weight of the thyroid is but slightly lower than in stillborn children, while the thyroglobulin is less, and that iodine is absent both in the inanition cases and in stillborn children.

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